AWARD NUMBER:	W81XWH-14-1-0112
TITLE:	Hemorrhage control for major traumatic vascular injuries
PRINCIPAL INVESTIGATOR:	John B. Holcomb, M.D.
CONTRACTING ORGANIZATION:	University of Texas Health Science Center at Houston Houston, TX 77225
REPORT DATE:	October 2016
TYPE OF REPORT:	Annual Report
PREPARED FOR:	U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012
DISTRIBUTION STATEMENT:	Approved for Public Release; Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	15 Sep 2015 – 14 Sep 2016

4. TITLE AND SUBTITLE
Hemorrhage control for major traumatic vascular injuries

5a. CONTRACT NUMBER
W81XWH-14-1-0112

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
John B. Holcomb, M.D.

E-Mail: john.holcomb@uth.tmc.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The University of Texas Health Science
Center at Houston
7000 Fannin Street, FL 2
Houston, TX 77030-5400

8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The objective of this proposed study is to systematically define the clinical and logistical issues surrounding traditional open vascular surgery and catheter-based hemorrhage control. The hypothesis is that minimally invasive, device-driven and expert-led NCTH control techniques improve survival compared to traditional open vascular surgery. This project will achieve the following aims: 1) Determine current practice patterns for the treatment of patients with NCTH among 4 clinical sites using a retrospective study design (Phase 1a); 2) Conduct a 2-day Delphi Panel meeting of military and civilian experts to gain consensus regarding anatomic, technology, credentialing, competency, and training issues for catheter-based hemorrhage control (Phase 1b); 3) Conduct a prospective 4-site observational study to test the hypothesis that less-invasive device-driven and expert-led hemorrhage control techniques are associated with improved survival in NCTH patients and strengthen the evidence base to inform future development of catheters, devices, and training required for surgeons for catheter-based hemorrhage control (Phase 2). At the end of Y2, the retrospective study has been completed, the Delphi Meeting has been held and a manuscript describing the results has been drafted. In addition, the prospective study will be initiated in Y3Q1 and regulatory approvals are in place or pending at all sites.

15. SUBJECT TERMS
Trauma, vascular, hemorrhage, Non-compressible Torso Hemorrhage, coagulation, mortality

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	153	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Page

INTRODUCTION

On September 30, 2014, the U.S. Army Medical Research Acquisition Activity (USAMRAA) awarded a 2-year contract to the University of Texas Health Science Center at Houston (UTHealth). This 2-year, 2-phase project will systematically define the clinical and logistical issues surrounding traditional open vascular surgery and catheter-based hemorrhage control for non-compressible torso hemorrhage (NCTH). The hypothesis is that minimally invasive, device-driven and expert-led NCTH control techniques improve survival compared to traditional open vascular surgery. In addition to UTHealth, Baylor College of Medicine, the University of Texas Health Science Center at San Antonio (UTHSCSA) and the San Antonio Military Medical Center (SAMMC)/US Army Institute of Surgical Research (USAISR) are collaborating.

KEYWORDS
Trauma, Vascular, Hemorrhage, Non-compressible Torso Hemorrhage, Coagulation, Mortality

ACCOMPLISHMENTS

What were the major goals of the project?

Calendar Year 2014-2015 Goals/Milestones – Phase I

1. Obtain DOD HPRO and local institutional review board (IRB) Approvals
2. Conduct retrospective data collection
3. Analysis of retrospective data
4. Hold Delphi Meeting

Calendar Year 2015-2016 Goals/Milestones – Phase II

5. Obtain regulatory amendment approvals for prospective study
6. Conduct prospective observational study
7. Data Analysis/Publications

What was accomplished under these goals?

Milestone 1: Obtain USAMRMC HRPO and participating sites' IRB approvals

Y1Q1 UT Houston IRB approval for the retrospective study was received 18-NOV-2014. We submitted the USAMRMC Human Research Protections Office (HRPO) application on 02-DEC-2014 for review and approval. We also sent the UTHealth IRB approval and study documents to participating sites to submit to their local IRB review and approval. Baylor College of Medicine (BCM) and the University of Texas Health Science Center at San Antonio (UTHSCSA) submitted their local IRB applications in Q1.

Y1Q2 USAMRMC HRPO approval for the retrospective study at the UTHealth site was obtained 23-JAN-2015. UTHSCSA obtained their local IRB approval on 12-MAR-2015. BCM also received local IRB approval on 10-APR-2015. San Antonio Military Medical Center (SAMMC) requested that their site be changed to the US Army Institute of Surgical Research (USAISR) because USAISR had more developed human subjects and contracting processes. USAISR submitted documents to their IRB in Q2.

Y1Q3 UTHSCSA received HRPO approval for the retrospective study on 27-MAR-2015 and BCM received HRPO approval on 20-APR-2015.

Y1Q4 USAISR received local IRB and HRPO approval on 22-June-2015. UTHealth received local IRB approval for their continuing review on 31-AUG-2015.

Y2Q1 UTHealth received HRPO continuing review acknowledgement for the retrospective study on 09-OCT-2015.

Y2Q2 BCM and UTHSCSA received continuing review approval for the retrospective study from their local IRBs on 19-JAN-2016 and 17-FEB-2016, respectively.

Y2Q3 UTHealth received approval for the retrospective study continuing review on 23-MAY-2016. UTHSCSA and BCM continuing review acknowledgments for the retrospective study were also received from HRPO on 04-APR-2016 and 22-MAR-2016, respectively. USAISR received IRB and HRPO approval and acknowledgement of continuing review on 18-JUN-2016.

Y2Q4 UTHealth received acknowledgement of continuing review for the retrospective study on 17-AUG-2016. All IRB and HRPO documents for the retrospective study can be found in Appendix 1.

Milestone 2: Initiate retrospective data collection study.

Y1Q1 Before the UTHealth IRB submission, we had a series of internal meetings as well as phone calls and emails with external investigators to discuss, revise, and finalize the protocol and case report forms for the retrospective study. The protocol and case report forms were finalized as of 15-NOV-2014. We also submitted information and study documents to UTHealth's Sponsored Projects Administration in order to begin drafting of the subcontracts for the three external sites as the next step to initiating data collection.

Y1Q2 The subcontracts with the three sites were drafted by UTHealth's Sponsored Projects Administration and sent to the three external sites as the first step to initiating data collection. The subcontracts were sent to the sites on 07-JAN-2015. Contract negotiation has taken longer than expected and at the end of Y1Q2, all three subcontracts were not yet executed. USAISR has requested a Cooperative Research and Development Agreement (CRADA) and a Data Use Agreement (DUA) for this study instead of the standard Federal Demonstration Partnership (FDP) contract we use for all other sites and projects. We expect that the contracts for BCM and UTHSCSA will be executed in early Q3. Because we have not received approval from the GOR for the change in PI for USAISR, we cannot move forward with the CRADA; however, the DUA can move forward. We have developed a REDCap application for the Phase 1 retrospective study, including a data dictionary, codebook and data entry forms. We are finalizing this database application. Once completed, UTHealth will start entering data into the application.

Y1Q3 UTHealth, UTHSCSA and BCM have begun the trauma registry query and retrospective data review. We received approval from the GOR for the change in PI and research site to USAISR. Contract negotiations continue with USAISR because they are using a Cooperative Research and Development Agreement (CRADA) instead of the standard Federal Demonstration Partnership (FDP) contract we developed for all sites. The Data Use Agreement (DUA) that ISR also required has been executed by both parties. The Program Manager at USISR contacted UTHealth on 25-June-2015 to request additional documents be sent to the Contract Officer at USAMRAA in order for the change in site to take effect. UTHealth sent the documents to her on 29-JUNE-2015. The REDCap application has been finalized and data entry into the system has begun.

Y1Q4 UTHealth requested a status update from the Contract Office at USAMRAA on 13-July-2015, and a response was received on 22-JULY-2015 stating that a modification was being prepared to change the study site. We received a request for additional documents on 08-OCT-2015 from USAMRAA.

Y2Q1 UTHealth, UTHSCSA and BCM completed trauma registry query and retrospective data review and data entry in Y2Q1. 239 patients from UTHealth, 189 from BCM, and 208 from UTHSCSA were enrolled. The Cooperative Research and Development Agreement (CRADA) between UTHealth and USAISR was also fully executed in Y2Q1. USAISR entered registry

information on all of their eligible patients (N=51) and are continuing to enter additional detailed data from the medical record abstraction.

Y2Q2 USAISR completed retrospective study data entry in Y2Q2. A total of 683 for the four sites were therefore available for analysis. This number was considerably less than the expected total for enrollment (n=3500) due to the operationalization of the eligibility criteria. The eligibility criteria from both the proposal and the IRB-approved protocol were:

Inclusion Criteria

To be eligible, subjects must meet all of the following:

1) Has NCTH defined as
    a. Named axial torso vessel disruption
    b. Solid organ injury with AIS ≥ 4 (liver, kidney, or spleen) plus concomitant shock or immediate operation
    c. Thoracic cavity injury (including lung)
    d. Pelvic fracture with ring disruption
2) Estimated age of 15 years or older or greater than/equal to weight of 50 kg if age unknown
3) Admitted to one of four participating Level 1 trauma centers

Exclusion Criteria

Subjects will be excluded of they meet one or more of the following:

1) Patients who are <15 years old or under 50 kg body weight if age unknown
2) Known pregnancy reported by EMS personnel
3) Isolated hip fractures
4) Injury resulting from a fall from standing

For the original submitted grant proposal, we received data from all 4 sites in order to estimate the potential number of patients we would be able to enroll in the retrospective using these inclusion and exclusion criteria. Using these criteria only, we estimated that we would enroll 3500 patients. However, in order to operationalize these criteria for the retrospective study using site trauma registries to identify appropriate patients and to get detailed information regarding the specific vessels of interest, the following rules were used at all 4 sites:

a. Run the following inclusions/exclusions first:
    i. Inclusions:
        1. Age 15 or older
        2. Admitted
        3. Time of injury < 12 hours from admission
            a. Not all of our patients have a time of injury in the registry, so we also used the date/time of EMS notification to try to catch any of those patients
    ii. Exclusions:
        1. Prisoners
        2. Isolated hip fractures
        3. Injury resulting from a fall from standing (< 6 feet)
        4. Prisoners, defined as those who have been directly admitted from a correctional facility

b. Use that data set to separately find the patients with abdominal, thoracic, and pelvic injuries
    i. Abdominal
        1. We searched for patients with AIS >= 3 plus base deficit > 4
        2. We searched for patients with AIS >= 3 plus immediate operation (limited it to patients that went directly from the ER to the OR within 90 minutes of arrival)
        3. We then combined those two lists
    ii. Thoracic
        1. We searched for patients with AIS >= 3 plus base deficit > 4
        2. We searched for patients with AIS >= 3 plus immediate operation (limited it to patients that went directly from the ER to the OR within 90 minutes of arrival)
        3. We then combined those two lists
    iii. Pelvic
        1. We searched for patients with AIS05 codes equal to: 856161.3, 856162.4, 856163.4, 856164.5, 856171.4, 856172.4, 856173.5, or 856174.5
    iv. Combine the above 3 lists (abdominal, thoracic, and pelvic)
c. Use that data set to separately find the patients with named axial torso vessel disruption using both AIS codes and ICD9 codes (to try to find as many as possible)
    i. AIS codes
        1. Thoracic arteries: 420206.4, 420208.4, 420210.5, 420216.5, 420218.6, 420404.3, 420406.3, 420408.4, 421004.3, 421006.3, 421008.5, 421009.6, 421404.3, 421406.3, 421408.4, 422004.2, 422006.2, 422008.3
        2. Thoracic veins: 420602.3, 420604.3, 420606.4, 420608.5, 421202.3, 421204.3, 421206.5, 421207.6, 421602.3, 421604.3, 421606.4, 421802.3, 421804.3, 421806.4, 421808.5, 422202.2, 422204.2, 422206.3
        3. Abdominal arteries: 520204.4, 520206.4, 520208.5, 520404.3, 520406.4, 520408.5, 520604.3, 520606.3, 520608.4, 521104.3, 521106.3, 521108.4, 521404.3, 521406.3, 521408.4, 541828.5
        4. Abdominal veins: 520802.3, 520804.3, 520806.4, 521002.2, 521004.2, 521006.3, 521202.3, 521204.3, 521206.4, 521602.3, 521604.3, 521606.4
        5. Common carotid arteries: 320206.3, 320208.3, 320209.3, 320210.4, 320211.4, 320212.4, 320213.4, 320214.5, 320215.5, 320216.3, 320217.3, 320218.4, 320219.4
    ii. ICD9 codes
        1. Thorax: 901.0, 901.1, 901.2, 901.3, 901.41, 901.42
        2. Abdomen: 902.0, 902.10, 902.20, 902.22, 902.23, 902.25, 902.31, 902.33, 902.41, 902.42, 902.53, 902.54
        3. Common carotid: 900.01
    iii. Combine the AIS and ICD9 lists and produced our final patient list.

Using these rules to generate the sampling frame for patients, further exclusions were made if no specifically-named vessels were reported in the medical record. In the prospective study, we will be able to include solid organ injuries as well as vessel injuries.

Y2Q3 We initiated a study of CT data for vascular injuries in order to begin collecting data for questions we had originally planned to address in the prospective study. This substudy uses data only from UTHealth, where we have adequate image storage capabilities, and is approved under the retrospective study UTHealth IRB and HRPO approvals. The plan for this substudy is to accurately quantify the applicable vascular morphometry of the human torso, which can be done with images previously stored during the retrospective study. For the scan-based measurements, standard imaging software is used to measure diameter and length of the torso vessels and relative distances between major aortic branch vessels as related to aortic zones defined by Stannard, et al. We are also including a CT measurement component in the prospective study at UTHealth to continue this work.

Y2Q4 Data collection, entry and cleaning for the substudy of CT images for vascular injuries was largely completed in Y2Q4. One more field for 100 patients remains to be entered and will be completed in Y3Q1. We also negotiated Data Use Agreements (DUAs) with Madigan Army Medical Center (PI: COL Matthew Martin) and with Denver Health Medical Center (PI: Charles Fox) for their use of the retrospective study data. Both were executed early in Y3Q1.

<u>Milestone 3: Analysis of retrospective data</u>

Y2Q1 We identified a Co-Investigator Statistician, Stacia deSantis, PhD, who worked on preliminary statistical analysis code and programs. She obtained access to the dataset, the data dictionary, the protocol, and updated the statistical plan with assistance from a statistical programmer (T. Jay Greene, MS).

Y2Q2 Data analysis for the Delphi Meeting was completed during this quarter. Additional analysis was undertaken during this quarter as a result of suggestions made at the Delphi Meeting. These analyses will be reported in an upcoming manuscript. Additionally, all attendees of the Delphi Meeting were offered the opportunity to analyze the retrospective data. We are currently working with these external institutions and negotiating Data Use Agreements (DUAs) with them. Our goal is that additional manuscripts and/or abstracts will be submitted as a result of sharing these important data.

Y2Q3 The additional analyses initiated last quarter are ongoing. These analyses will be reported in an upcoming manuscript. Two external institutions (Madigan Army Medical Center and Denver Health Medical Center) requested the retrospective data for their own analysis. The UTHealth Sponsored Projects office completed the draft of the Data Use Agreement, which was sent to the two institutions for negotiation and execution in June 2016.

Y2Q4 We submitted an abstract of the retrospective study to the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting and it was accepted for an oral presentation at the meeting in January. We also drafted a manuscript for the main results of the retrospective study

during Y2Q4 and it will be finalized in Y3Q1. The abstract and manuscript draft are included in Appendix 2. Negotiation of the two DUAs continued this quarter.

Milestone 4: Hold Delphi Meeting

Y2Q1 We updated the list of 20 potential Delphi Panel meeting attendees and received input on additional potential attendees from Col. Todd Rasmussen, an expert in non-compressible torso hemorrhage

Y2Q2 The Delphi Panel Meeting was held on March 7, 2016 at the University of Texas Health Science Center at Houston. A total of 27 people attended the meeting. Attendees included the site investigators and coordinators, trauma and vascular surgeons from civilian and military institutions, and the Houston Data Coordinating Center. The group reviewed the results of the retrospective study and provided input for the upcoming Phase II prospective, observational study. See the Y2Q2 report for the agenda and review of retrospective data used at the Delphi Meeting, notes from the meeting, and a list and picture of participants.

Y2Q3 Milestone complete, nothing to report

Y2Q4 Milestone complete, nothing to report

Milestone 5: Obtain regulatory amendment approvals for prospective study

Y2Q2 We refined a draft of the prospective study protocol based on recommendations and comments at the Delphi Meeting.

Y2Q3 We finalized the Phase II prospective protocol with the other site PIs and staff. The protocol was submitted to the UTHealth IRB on 27-MAY-2016.

Y2Q4 UTHealth received IRB approval on 20-JUL-2016. BCM submitted the protocol to their IRB during Y2Q4. Approval for BCM was received 21-SEP-2016. UTHSCSA applied for IRB reciprocity during this quarter and received approval from the UTHealth IRB on 12-SEP-2016 (see documents in Appendix 3). UTHealth and UTHSCSA submitted their approval documents to HRPO for review and approval was received on 05-OCT-2016. USAISR prepared their documents for submission to the MRMC IRB/HRPO next quarter.

Milestone 6: Conduct prospective observational study

Y2Q4 We drafted modifications of subawards for BCM and UTHSCSA to extend the date of contract and add the Phase II funds. Both contracts have been executed (BCM on 29-SEP-2016 and UTHSCSA on 30-SEP-2016). We are negotiating a CRADA modification with USAISR for the change in PI from LTC Kevin Chung to LTC Jennifer Gurney. It was signed by UTHealth on 20-SEPT-2016 and we are awaiting signature and full execution by USAISR. In preparation of study initiation, we developed a draft of the Manual of Operations and have circulated it to the 3 external sites for review and comment (see Appendix 4).We expect to enroll patients in Y3Q1.

Milestone 7: Data Analysis/Publications

Y2Q2 We worked on finalizing data analyses and developing a manuscript for the retrospective study.

Y2Q3 We continued to work on finalizing data analyses and developing a manuscript for the retrospective study.

Y2Q4 We submitted an abstract of the retrospective study to the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting on 01-JUL-2016 and it was accepted on 01-AUG-2016 for oral presentation at the meeting. We also drafted a manuscript for this presentation during Y2Q4.

What opportunities for training and professional development has the project provided?
Nothing to report.

How were the results disseminated to communities of interest?
Nothing to report. Results will be disseminated at the end of the project.

What do you plan to do during the next reporting period to accomplish the goals?
Milestone 1: Obtain USAMRMC HRPO and participating sites' IRB approvals
During Y3 of the project, we will ensure that the sites submit continuing reviews for the retrospective study to their local IRBs and HRPO in order to continue data analysis and manuscript development. We will also ensure that any Delphi Meeting attendees who have signed DUAs in order to perform their own data analysis will obtain appropriate regulatory approvals before data is released to them.

Milestone 2: Initiate retrospective data collection study
Milestone complete.

Milestone 3: Analysis of retrospective data
Analysis of the retrospective data will continue for development of additional secondary manuscripts. Also, data analysis for the CT image substudy will be finalized in Y3Q1.

Milestone 4: Hold Delphi Meeting
Milestone complete.

Milestone 5: Obtain regulatory amendment approvals for prospective study
UTHealth and UTHSCSA have already received HRPO approval for the prospective study as of 05-OCT-2016. We expect BCM to receive HRPO approval for the prospective study in Y3Q1. USAISR will submit their site-specific protocol for the prospective study to the MRMC IRB//HRPO in Y3Q1. During Y3 of the project, we will ensure that the sites submit continuing reviews for the prospective study to their local IRBs and HRPO in order to complete the study.

Milestone 6: Conduct prospective observational study
We will initiate the prospective study at all 4 sites during Y3Q1.

Milestone 7: Data Analysis/Publications

The main results of the retrospective study will be presented at EAST in January 2014. A manuscript for this presentation was drafted during Y2Q4 and it will be finalized and submitted in Y3Q1/2.

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfers?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

We are approximately 1 year behind due to various issues from early in the project that have since been solved. Since we have the 1 year extension without funds, this should not cause a problem and we will begin enrolling in the prospective study in Y3Q1 and plan to complete it before the end of the EWOF.

Changes that had a significant impact on expenditures

Because of a later start than anticipated, sites spent their Y1 funding slower than expected. At UTHealth, we also decreased paid effort on the project between July and September while awaiting regulatory approvals in order to save any remaining funding for the prospective study. BCM and UTHSCSA recently received their Phase II funding in a contract modification in anticipation of the prospective study starting soon, therefore all Phase II funding for these sites is available. USAISR submitted 1 invoice for the retrospective study in February 2016 for the full amount of Phase I funding. However, the invoice was submitted with no documentation of expenditures. Because the CRADA is cost-reimbursable, UTHealth requested the documentation, but none has been received to date. UTHealth reminded USAISR to send the documentation or a revised invoice in August 2016.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

PRODUCTS

Publications, conference papers, and presentations

Nothing to report.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
What individuals have worked on the project?

Name:	John Holcomb, MD
Project Role:	Principal Investigator
Nearest Person Months Worked:	1
Contribution to Project:	Dr. Holcomb oversees all aspects of study management and execution for both the retrospective and prospective studies. He oversees all study staff, regulatory submissions, patient screening, subject enrollment, and data collection. He actively communicates with all clinical sites for this study to coordinate administration across institutions and to ensure accurate and timely data collection and transfer.
Funding Source:	DOD W81XWH-14-1-0112

Name:	Erin Fox, PhD
Project Role:	Co-Investigator; Project Manager
Nearest Person Months Worked:	2
Contribution to Project:	Dr. Fox oversees the day-to-day communication and overall study coordination for both the retrospective and prospective multisite studies. She ensures timely and accurate reporting, including financial and interim research reports. She participated in the creation of the data management system and the Manual of Operation, data cleaning and integration, and coordination of requested data to research investigators in the retrospective study and will perform similar duties in the prospective study. She coordinated the subcontracts and budgets for the research sites. Dr. Fox is also involved with the analysis of data, interpretation of results, and development of manuscripts for this project.
Funding Source:	DOD W81XWH-14-1-0112

Name:	Charles Wade, Ph.D.
Project Role:	Co-Investigator
Nearest Person Months Worked:	1
Contribution to Project:	Dr. Wade participated in the creation of the data management system and the Manual of Operation, data cleaning and integration, and coordination of requested data to research investigators.
Funding Source:	DOD W81XWH-14-1-0112

Name:	Jeanette Podbielski, R.N.
Project Role:	Clinical Program/Regulatory Director
Nearest Person Months Worked:	1

Contribution to Project:	Ms. Podbielski managed all regulatory aspects of this study. She assisted with study coordination as well as IRB preparation and submission. She managed the activities of the Research Coordinator and Assistant. Ms. Podbielski is the main point of contact for the external sites for regulatory issues, patient enrollment, and data collection.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Garrett Jost
Project Role:	Research Coordinator
Nearest Person Months Worked:	2
Contribution to Project:	Mr. Jost assisted with all aspects of study coordination, including the attainment and maintenance of all necessary regulatory approvals and guidelines as well as patient enrollment, data collection, data entry, and answering queries at the UTHealth site for the retrospective study. Mr. Jost will have similar responsibilities on the prospective study.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Amanda Haymaker
Project Role:	Research Assistant
Nearest Person Months Worked:	1
Contribution to Project:	Ms. Haymaker assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the retrospective study and will have similar duties in the prospective study.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Marc Dipasupil
Project Role:	Research Assistant
Nearest Person Months Worked:	1
Contribution to Project:	Mr. Dipasupil assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the retrospective study and will have similar duties in the prospective study.
Funding Source:	DOD W81XWH-14-1-0112
Name:	Jeff Tomasek, MD
Project Role:	Research Assistant
Nearest Person Months Worked:	2
Contribution to Project:	Dr. Tomasek identified an appropriate population of patients through the trauma registry, set-up the REDCap database, provided training for the external sites, and coordinates the collection of data from the four clinical

	sites into the central database used for analysis of the retrospective study. He will have similar duties on the prospective study and has already set up the REDCap database for it.
Funding Source:	DOD W81XWH-14-1-0112

Name:	Donna Grayson
Project Role:	Administrator
Nearest Person Months Worked:	1
Contribution to Project:	Ms. Grayson assisted in subcontracting, billing, budgeting and the preparation of financial and interim report reports.
Funding Source:	DOD W81XWH-14-1-011

Name:	Stacia DeSantis, PhD
Project Role:	Co-Investigator (Statistician)
Nearest Person Months Worked:	1
Contribution to Project:	Dr. DeSantis is the lead statistician for this project. She oversees all data management and analysis for both the retrospective and prospective studies.
Funding Source:	DOD W81XWH-14-1-0112

Name:	T. Jay Greene, MS
Project Role:	Graduate Research Assistant (Statistical Programmer)
Nearest Person Months Worked:	2
Contribution to Project:	Mr. Green acts as the statistical programmer for both the retrospective and prospective studies and is supervised by Dr. DeSantis.
Funding Source:	DOD W81XWH-14-1-0112

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The project entitled "Treatment of Adult Severe Traumatic Brain Injury Using Autologous Bone Marrow Mononuclear Cells" ended and Dr. Holcomb is no longer contributing effort to it. New projects include the following:

Title:	The PROspective Observational Vascular Injury Trial (PROOVIT)
Time Commitment:	John Holcomb, 2% as Site PI
Supporting Agency	National Trauma Institute/DOD/Army Medical Research
Agency Contact	Jennifer Shankle, Grants Specialist, Jennifer.e.shankle.civ@mail.mil
Performance Period	12/2015-11/2017
Project Goals	The major goal of this project is to establish a prospective, multicenter, observational study through the AAST Multicenter Trials Committee.
Overlap	No scientific or effort overlap

What other organizations were involved as partners?
Baylor College of Medicine
Houston, TX
Research collaborator

University of Texas Health Science Center at San Antonio
San Antonio, TX
Research collaborator

US Army Institute of Surgical Research
San Antonio, TX
Research collaborator

SPECIAL REPORTING REQUIREMENTS
Quad Chart uploaded as Appendix 5.

APPENDICES

Appendix 1. IRB/HRPO documents from Y2 for the retrospective study

UTHealth
The University of Texas
Health Science Center at Houston

Committee for the Protection of Human Subjects
6410 Fannin Street, Suite 1100
Houston, Texas 77030

John Holcomb, MD, FACS
UT-H - MS - Surgery

NOTICE OF CONTINUING REVIEW APPROVAL May 23, 2016

HSC-GEN-14-0966 - *Hemorrhage Control for Major Traumatic Vascular InjuriesPhase I: A Retrospective Analysis of Non-Compressible Torso Hemorrhage*

PI: John Holcomb, MD, FACS

PROVISOS: Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consents, etc.

NOTE: If this study meets the federal registration requirements and this is an investigator-initiated study, or if the PI is the study sponsor or holds the IND/IDE applicable to this study, and no one else has registered this trial on the national registry, you are required to register this trial on the national registry at www.clinicaltrials.gov in order to publish results in any of the key peer-reviewed journals. For further information write to clinicaltrials@uth.tmc.edu or call 713-500-7909.

APPROVED: By Expedited Review and Approval

REVIEW DATE: 05/23/2016

APPROVAL DATE: 05/23/2016 **EXPIRATION DATE**: 04/30/2017

CHAIRPERSON: Rebecca Lunstroth, JD 

Upon review, the CPHS finds that this research is being conducted in accord with its guidelines and with the methods agreed upon by the principal investigator (PI) and approved by the Committee. This approval, subject to any listed provisions and contingent upon compliance with the following stipulations, will expire as noted above:

CHANGES: The PI must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS: The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

RECORDS: The PI will maintain adequate records, including signed consent documents if required, in a manner which ensures subject confidentiality.

WE MAKE LIVES BETTER
UT HEALTH SCIENCE CENTER
SAN ANTONIO

February 17, 2016

To: Brian J. Eastridge, M.D. (eastridge@uthscsa.edu)
UTHSCSA

cc: Kristin Rocchi, R.N. (Rocchi@uthscsa.edu)

From: Institutional Review Board

Subject: **Expedited Approval of a Request to Continue Research (Reapproval)**

Protocol Number: HSC20150253H
Title: A Retrospective Analysis of Non-Compressible Torso Hemorrhage (NCTH)

Funding Type: Other Federal Funding (Non-HHS)**; Sponsor:** DoD, W81XWH-14-1-0112**; Grant Title(s):** Hemorrhage Control for Major Traumatic Vascular Injuries

Dear Principal Investigator,

Your progress report, dated January 16, 2016, was reviewed and approved by the Institutional Review Board on February 16, 2016. Your study has been approved to continue.

The new IRB expiration date: March 12, 2017. Your progress report must be submitted to the IRB Office 34 days before the IRB meeting that will occur before the study's expiration date.

In addition to the progress report, the following documents were reviewed: Signature Assurance Sheet; **Other:** UT Houston Cont. Rev 2015.

Your progress report included the following minor modifications that were also approved: No changes.

Affiliated institutions which are engaged in this research: UTHSCSA University Health System

Sincerely,

Research Compliance Coordinator
Research Protection Programs

Please retain this document in your IRB correspondence file

January 19, 2016

RAMYAR GILANI
BAYLOR COLLEGE OF MEDICINE
SURGERY: HCHD DIVISION

Baylor College of Medicine
Office of Research
One Baylor Plaza, 600D
Houston, Texas 77030
Phone: (713) 798-6970
Fax: (713) 798-6990
Email: irb@bcm.tmc.edu

H-36237 - PHASE I: A RETROSPECTIVE ANALYSIS OF NON-COMPRESSIBLE TORSO HEMORRHAGE (NCTH)

APPROVAL VALID FROM 1/19/2016 TO 1/4/2017

Dear Dr. GILANI

The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals (BCM IRB) is pleased to inform you that the research protocol named above was reviewed and approved by Expedited procedures on 1/5/2016 by Board 1.

The study may not continue after the approval period without additional IRB review and approval for continuation. You will receive an email renewal reminder notice prior to study expiration; however, it is your responsibility to assure that this study is not conducted beyond the expiration date.

Please be aware that only IRB-approved informed consent forms may be used when written informed consent is required.

Any changes in study or informed consent procedure must receive review and approval prior to implementation unless the change is necessary for the safety of subjects. In addition, you must inform the IRB of adverse events encountered during the study or of any new and significant information that may impact a research participants' safety or willingness to continue in your study.

The BCM IRB is organized, operates, and is registered with the United States Office for Human Research Protections according to the regulations codified in the United States Code of Federal Regulations at 45 CFR 46 and 21 CFR 56. The BCM IRB operates under the BCM Federal Wide Assurance No. 00000286, as well as those of hospitals and institutions affiliated with the College.

Sincerely yours,

Jalmira Habib

GABRIEL HABIB, M.D.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

DEPARTMENT OF THE ARMY
HEADQUARTERS, US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
810 SCHREIDER STREET
FORT DETRICK, MD 21702-5000

REPLY TO
ATTENTION OF

MCMR-RPI 18 June 2016

MEMORANDUM FOR RECORD

SUBJECT: Continuing Review and Amendment #1 Approval for the Protocol, "Hemorrhage Control for Major Traumatic Vascular Injuries Phase I: A Retrospective Analysis of Non-Compressible Torso Hemorrhage (NCTH)," Principal Investigator: LTC Kevin Chung, MC, US Army Institute of Surgical Research (USAISR), Joint Base San Antonio, Fort Sam Houston, TX, in Support of the Proposal "Hemorrhage Control for Major Traumatic Vascular Injuries," Proposal Principal Investigator: John Holcomb, MD, University of Texas Health Science Center, Houston, Proposal Number 13057176, Award Number W81XWH-14-1-0112, HRPO Log Number A-18067, USAISR Protocol H-15-004, IRB Protocol Number M-10446

1. The Headquarters, US Army Medical Research and Materiel Command Institutional Review Board (HQ USAMRMC IRB) initially approved the above-referenced minimal risk research protocol via expedited review procedure on 21 June 2015 with waiver of informed consent and HIPAA authorization.

2. The HQ USAMRMC IRB received a continuation report and amendment #1 on 26 May 2016. The study is open for data analysis only.

3. The protocol and continuation report were reviewed via an expedited review procedure in accordance with 32 CFR 219.110(a,b). The protocol remains in compliance with Federal, DOD, and US Army human subjects protection requirements. The research protocol is approved for a period of one year, expiring 20 June 2017. Note that the continuing review date is set based on the current expiration date of 20 June 2016.

4. Amendment #1 removes Lt Col Jeremy Cannon and Mr. Don Simpson from the USISR study team and extends the length of time required to complete the research to three years.

5. There are no new or additional risks to participants from the modifications beyond those identified in the previously approved protocol. The protocol amendment is approved via expedited review as IRB Amendment #1 as allowed under 32 CFR 219.110(a,b).

6. Amendment #1 approves Site-specific Protocol Version 2, dated 09 May 2016.

MCMR-RPI
SUBJECT: Continuing Review and Amendment #1 Approval for the Protocol, "Hemorrhage Control for Major Traumatic Vascular Injuries Phase I: A Retrospective Analysis of Non-Compressible Torso Hemorrhage (NCTH)," Principal Investigator: LTC Kevin Chung, MC, US Army Institute of Surgical Research (USAISR), Joint Base San Antonio, Fort Sam Houston, TX, in Support of the Proposal "Hemorrhage Control for Major Traumatic Vascular Injuries," Proposal Principal Investigator: John Holcomb, MD, University of Texas Health Science Center, Houston, Proposal Number 13057176, Award Number W81XWH-14-1-0112, HRPO Log Number A-18067, USAISR Protocol H-15-004, IRB Protocol Number M-10446

7. Please note the following requirements:

a. Submit all proposed changes to the study for review and approval by the HQ USAMRMC IRB before initiating the changes.

b. Promptly report to the HQ USAMRMC IRB:

(1) All unanticipated problems involving risks to subjects or others and related serious adverse events.

(2) Any protocol deviation that affects subjects' safety or rights and/or the integrity of the study.

c. Submit a continuation report, a copy of the current protocol and supporting documents to the HQ USAMRMC IRB in sufficient time to ensure review and approval on or before 20 June 2017.

d. Submit a final study report and request to close the protocol upon completion of all research activities.

8. The IRB Office point of contact for this action is Debra DePaul, RN, MSN, General Dynamics Information Technology Corporation, at 301-619-2620 or debra.depaul.ctr@mail.mil.

LTC JAY R. BUCCI, MD, PhD
Chair
Headquarters, US Army Medical Research
and Materiel Command
Institutional Review Board

From:	Soto, Joseph D CTR USARMY MEDCOM USAMRMC (US)
To:	Holcomb, John B
Cc:	Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Toups, Krystal R; Podbielski, Jeanette M; Doan, Robert T Jr CIV USARMY MEDCOM USAMRAA (US); Jorgensen, Shelley C CIV USARMY MEDCOM CDMRP (US); Stubbs, Susie Carolyn CTR USARMY MEDCOM (US); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US); Brosch, Laura R CIV USARMY MEDCOM USAMRMC (US); Soto, Joseph D CTR USARMY MEDCOM USAMRMC (US)
Subject:	A-18067.1a, Continuing Review Acknowledgment Memorandum (Proposal Log Number 13057176, Award Number W81XWH-14-1-0112) (UNCLASSIFIED)
Date:	Wednesday, August 17, 2016 3:52:27 PM

Classification: UNCLASSIFIED
Caveats: NONE

SUBJECT: Acknowledgement of the Continuing Review documents for the protocol, "Hemorrhage Control for Major Traumatic Vascular Injuries Phase 1: A Retrospective Analysis of Non-Compressible Torso Hemorrhage," Submitted by John B. Holcomb, MD, University of Texas Health Science Center, Houston, Texas, in Support of the Proposal, "Hemorrhage Control for Major Traumatic Vascular Injuries," Submitted by John B. Holcomb, MD, University of Texas Health Science Center, Houston, Texas, Proposal Log Number 13057176, Award Number W81XWH-14-1-0112, HRPO Log Number A-18067.1a

1. The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) approved the subject protocol on 23 January 2015.

2. The USAMRMC ORP HRPO received the University of Texas Health Science Center, Houston (UTHSCH) Committee for the Protection of Human Subjects (CPHS) approval on 26 July 2016. The UTHSCH CPHS approved continuation of the subject protocol on 23 May 2016; this approval will expire on 30 April 2017.

3. This correspondence serves to acknowledge HRPO receipt of the continuing review documents for the protocol. No further action related to this continuing review is needed. The documents in support of this continuing review will be placed in the HRPO file.

4. The Principal Investigator must provide the following post-approval submissions to the HRPO via email to Usarmy.detrick.medcom-usamrmc.other.hrpo-cr-documents@mail.mil. Failure to comply could result in suspension of funding.

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change in the IRB of Record, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the IRB is due no later than 30 April 2017. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) or mail to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

(6) Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRMC ORP HRPO. The report must include actions taken by the institution and the IRB.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

5. Please note: The USAMRMC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

6. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.

7. The HRPO point of contact for this action is Joseph Soto, Human Subjects Protection Scientist, at extension 301-619-3098/joseph.d.soto.ctr@mail.mil

Regards,

Joseph D. Soto
Human Subjects Protection Scientist
General Dynamics Information Technology (GDIT)
Human Research Protection Office (HRPO)
Office of Research Protections (ORP)
US Army Medical Research & Materiel Command (USAMRMC)
Fort Detrick, Maryland
Email: joseph.d.soto.ctr@mail.mil
Phone: 301-619-3098 or DSN 343-3098
Fax: 301-619-4165 or DSN 343-4165

Mailing Address:
Commanding General
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RPH/Joseph Soto
810 Schreider Street
Frederick, Maryland 21702-5012
US Army Medical Research and Materiel Command

From:	Soto, Joseph D CTR USARMY MEDCOM USAMRMC (US)
To:	Eastridge, Brian
Cc:	Toups, Krystal R; Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Holcomb, John B; Podbielski, Jeanette M; Doan, Robert T Jr CIV USARMY MEDCOM USAMRAA (US); Jorgensen, Shelley C CIV USARMY MEDCOM CDMRP (US); Englar, Nancy E CTR USARMY USAMC (US); Brosch, Laura R CIV USARMY MEDCOM USAMRMC (US); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US); Stubbs, Susie Carolyn CTR USARMY MEDCOM (US); Soto, Joseph D CTR USARMY MEDCOM USAMRMC (US)
Subject:	A-18067.b, Continuing Review Acknowledgment Memorandum (Proposal Log Number 13057176, Award Number W81XWH-14-1-0112) (UNCLASSIFIED)
Date:	Wednesday, April 06, 2016 9:58:30 AM

Classification: UNCLASSIFIED
Caveats: NONE

SUBJECT: Acknowledgement of the Continuing Review documents for the protocol, "Hemorrhage Control for Major Traumatic Vascular Injuries Phase I: A Retrospective Analysis of Non-Compressible Torso Hemorrhage (NCTH)," Submitted by Brian J. Eastridge, MD, University of Texas Health Science Center San Antonio, San Antonio, Texas, in Support of the Proposal, "Hemorrhage Control for Major Traumatic Vascular Injuries," Submitted by John B. Holcomb, MD, University of Texas Health Science Center at Houston, Houston, Texas, Proposal Log Number 13057176, Award Number W81XWH-14-1-0112, HRPO Log Number A-18067.b

1. The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) approved the subject protocol on 27 March 2015.

2. The USAMRMC ORP HRPO received the University of Texas Health Science Center, San Antonio (UTHSCSA) Institutional Review Board (IRB) approval on 22 March 2016. The UTHSCSA IRB approved continuation of the subject protocol on 16 February 2016; this approval will expire on 12 March 2017.

3. This correspondence serves to acknowledge HRPO receipt of the continuing review documents for the protocol. No further action related to this continuing review is needed. The documents in support of this continuing review will be placed in the HRPO file.

4. The Principal Investigator must provide the following post-approval submissions to the HRPO via email to Usarmy.detrick.medcom-usamrmc.other.hrpo-cr-documents@mail.mil. Failure to comply could result in suspension of funding.

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change in the IRB of Record, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the IRB is due no later than 12 March 2017. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) or mail to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

(6) Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRMC ORP HRPO. The report must include actions taken by the institution and the IRB.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

5. Please note: The USAMRMC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

6. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.

7. The HRPO point of contact for this study is Joseph Soto, Human Subjects Protection Scientist, at extension 301-619-3098/joseph.d.soto.ctr@mail.mil

Regards,

Joseph D. Soto
Human Subjects Protection Scientist
General Dynamics Information Technology (GDIT)
Human Research Protection Office (HRPO)
Office of Research Protections (ORP)
US Army Medical Research & Materiel Command (USAMRMC)
Fort Detrick, Maryland
Email: joseph.d.soto.ctr@mail.mil
Phone: 301-619-3098 or DSN 343-3098
Fax: 301-619-4165 or DSN 343-4165

Mailing Address:
Commanding General
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RPH/Joseph Soto
810 Schreider Street
Frederick, Maryland 21702-5012

From:	Soto, Joseph D CTR USARMY MEDCOM USAMRMC (US)
To:	rgilani@bcm.tmc.edu
Cc:	Toups, Krystal R; Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Holcomb, John B; Podbielski, Jeanette M; Nowell, Lance L CIV USARMY MEDCOM USAMRAA (US); Jorgensen, Shelley C CIV USARMY MEDCOM CDMRP (US); Renner, Andrea K CTR USARMY MEDCOM CDMRP (US); regulatorycompliance@tatrc.org; Englar, Nancy E CTR USARMY USAMC (US); Brosch, Laura R CIV USARMY MEDCOM USAMRMC (US); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US); Stubbs, Susie Carolyn CTR USARMY MEDCOM (US); Soto, Joseph D CTR USARMY MEDCOM USAMRMC (US)
Subject:	A-18067.d, Continuing Review Acknowledgment Memorandum (Proposal Log Number 13057176, Award Number W81XWH-14-1-0112) (UNCLASSIFIED)
Date:	Tuesday, March 22, 2016 1:19:24 PM

Classification: UNCLASSIFIED
Caveats: NONE

SUBJECT: Acknowledgement of the Continuing Review documents for the protocol, "Hemorrhage Control for Major Traumatic Vascular Injuries Phase I: A Retrospective Analysis of Non-Compressible Torso Hemorrhage (NCTH)," Submitted by Ramyar Gilani, MD, Baylor College of Medicine, Houston, TX, in Support of the Proposal, "Hemorrhage Control for Major Traumatic Vascular Injuries," Submitted by John Holcomb, MD, University of Texas Health Science Center, Houston, TX, Proposal Log Number 13057176, Award Number W81XWH-14-1-0112, HRPO Log Number A-18067.d

1. The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) approved the subject protocol on 20 April 2015.

2. The USAMRMC ORP HRPO received the Baylor College of Medicine and Affiliated Hospitals (BCM) Institutional Review Board (IRB) approval on 21 January 2016. The BCM IRB approved continuation of the subject protocol on 19 January 2016; this approval will expire on 4 January 2017.

3. This correspondence serves to acknowledge HRPO receipt of the continuing review documents for the protocol. No further action related to this continuing review is needed. The documents in support of this continuing review will be placed in the HRPO file.

4. The Principal Investigator must provide the following post-approval submissions to the HRPO via email to Usarmy.detrick.medcom-usamrmc.other.hrpo-cr-documents@mail.mil. Failure to comply could result in suspension of funding.

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change in the IRB of Record, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the IRB is due no later than 4 January 2017. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) or mail to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

(6) Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRMC ORP HRPO. The report must include actions taken by the institution and the IRB.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

5. Please note: The USAMRMC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

6. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.

7. The HRPO point of contact for this study is Joseph Soto, Human Subjects Protection Scientist, at extension 301-619-3098/joseph.d.soto.ctr@mail.mil

Regards,

Joseph D. Soto
Human Subjects Protection Scientist
General Dynamics Information Technology (GDIT)
Human Research Protection Office (HRPO)
Office of Research Protections (ORP)
US Army Medical Research & Materiel Command (USAMRMC)
Fort Detrick, Maryland
Email: joseph.d.soto.ctr@mail.mil
Phone: 301-619-3098 or DSN 343-3098
Fax: 301-619-4165 or DSN 343-4165

Mailing Address:
Commanding General
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RPH/Joseph Soto
810 Schreider Street
Frederick, Maryland 21702-5012

Appendix 2. Abstract and draft manuscript from the retrospective study

Multicenter retrospective study of non-compressible torso hemorrhage: anatomic locations of bleeding and comparison of endovascular versus open approach

Chang R, Fox EE, Greene TJ, Eastridge BJ, Gilani R, Chung KK, DeSantis SM, DuBose JJ, Tomasek JS, Fortuna GR, Sams VG, Todd SR, Podbielski JM, Wade CE, Holcomb JB

Objective: To describe the anatomic location of truncal bleeding in patients presenting with non-compressible torso hemorrhage (NCTH) and to compare endovascular (ENDO) versus open (OPEN) management.

Methods: Retrospective study of adult trauma patients with NCTH admitted to 4 urban level 1 trauma centers in 2008-2012. Inclusion criteria: NCTH defined as named axial torso vessel disruption, AIS chest or abdomen ≥3 with shock (base excess <-4) or operation in ≤90 minutes, or pelvic fracture with ring disruption. Exclusion criteria included isolated hip fractures and falls from standing. After dividing patients into ENDO and OPEN groups based on the initial approach to control NCTH, a purposeful multivariate logistic regression model was used to test the hypothesis that ENDO was associated with reduced in-hospital mortality in NCTH patients.

Results: 560 patients with NCTH underwent ENDO (n=175, 31%) or OPEN (n=385, 69%). ENDO patients had more blunt trauma (95% vs 32%, $p<0.01$); were more severely injured (median ISS 34 vs 25, $p<0.01$); had increased time to intervention (median 295 vs 87 min, $p<0.01$); and had lower mortality (17% vs 31%, $p<0.01$) compared to OPEN. ED vital signs and presence of shock were similar ($p>0.05$). ENDO was used for a narrow range of vascular injuries, while OPEN injuries were more diverse (Table). Use of ENDO for NCTH increased from 23% in 2008 to 39% in 2012. After adjusting for age, mechanism, ISS, use of REBOA, and admission SBP, base excess, and platelet count, multivariate logistic regression found that ENDO was associated with decreased mortality compared to OPEN (OR 0.38, 95% CI 0.19 – 0.77).

Conclusion: ENDO was used in a relatively narrow range of bleeding control indications in this NCTH population. Although ENDO may reduce mortality in NCTH patients, significant group differences limit the generalizability of this finding.

Table. Anatomic location of NCTH

	ENDO (n=175)			OPEN (n=385)	
Ascending aorta, arch, and arch vessels	7	4.0%		33	8.6%
Superior vena cava	0	0.0%		14	3.6%
Internal thoracic arteries	0	0.0%		19	4.9%
Descending aorta	44	25.1%		16	4.2%
Pulmonary vessels	0	0.0%		10	2.6%
Abdominal aorta	2	1.1%		17	4.4%
Common hepatic & splenic arteries	14	8.0%		16	4.2%
Other abdominal visceral arteries	8	4.6%		49	12.7%
Abdominal visceral veins	2	1.1%		33	8.6%
Inferior vena cava	0	0.0%		56	14.5%
Renal arteries	14	8.0%		10	2.6%
Renal veins	0	0.0%		8	2.1%
Common & external iliac arteries	5	2.9%		24	6.2%
Internal iliac arteries & branches	73	41.7%		34	8.8%
Common, external, & internal iliac veins	3	1.7%		32	8.3%
Unknown/other	3	1.7%		14	3.6%

Multicenter retrospective study of non-compressible torso hemorrhage: anatomic locations of bleeding and comparison of endovascular versus open approach

Short title: NCTH hemorrhage

Ronald Chang, MD[a,b], Erin E. Fox, PhD[a,b], Thomas J. Greene, MS[c], Brian J. Eastridge, MD[d], Raymar Gilani, MD[e], Kevin K. Chung, MD[f,g], Stacia M. DeSantis, PhD[c], Joseph J. DuBose, MD[h], Jeffrey S. Tomasek, MD[a], Gerald R. Fortuna Jr., MD[h], Valerie G. Sams, MD[d,f], Samuel R. Todd, MD,[e] Jeanette M. Podbielski, BSN, RN[a], Charles E. Wade, PhD[a,b], John B. Holcomb, MD[a,b] and the NCTH Study Group.

a. Center for Translational Injury Research, University of Texas Health Science Center, Houston, TX
b. Department of Surgery, University of Texas Health Science Center, Houston, TX
c. Department of Biostatistics, School of Public Health, University of Texas Health Science Center, Houston, TX
d. Department of Surgery, University of Texas Health Science Center, San Antonio, TX
e. Department of Surgery, Baylor College of Medicine, Houston, TX
f. United States Army Institute of Surgical Research, Fort Sam Houston, TX
g. San Antonio Military Medical Center, San Antonio, TX
h. Department of Cardiothoracic and Vascular Surgery, The University of Texas Medical School at Houston

Corresponding author:

Ronald Chang, MD
6410 Fannin St.
Suite 1100
Houston, TX 77030
t: 713-500-6247
f: 713-500-0683
ronald.chang@uth.tmc.edu

Sponsors: The Non-Compressible Torso Hemorrhage (NCTH) study was sponsored by the U.S. Department of Defense (W81XWH-14-1-0112). RC is supported by a T32 fellowship from NIGMS (5T32GM008792).

Abstract:

Objective: To describe the anatomic location of truncal bleeding in patients presenting with non-compressible torso hemorrhage (NCTH) and to compare endovascular (ENDO) versus open (OPEN) management.

Methods: Retrospective study of adult trauma patients with NCTH admitted to 4 urban level 1 trauma centers in 2008-2012. Inclusion criteria: NCTH defined as named axial torso vessel disruption, AIS chest or abdomen ≥3 with shock (base excess <-4) or operation in ≤90 minutes, or pelvic fracture with ring disruption. Exclusion criteria included isolated hip fractures and falls from standing. After dividing patients into ENDO and OPEN groups based on the initial approach to control NCTH, a purposeful multivariate logistic regression model was used to test the hypothesis that ENDO was associated with reduced in-hospital mortality in NCTH patients.

Results: 560 patients with NCTH underwent ENDO (n=175, 31%) or OPEN (n=385, 69%). ENDO patients had more blunt trauma (95% vs 32%, p<0.01); were more severely injured (median ISS 34 vs 25, p<0.01); had increased time to intervention (median 295 vs 87 min, p<0.01); and had lower mortality (17% vs 31%, p<0.01) compared to OPEN. ED vital signs and presence of shock were similar (p>0.05). ENDO was used for a narrow range of vascular injuries (internal iliac arteries and blunt descending aortic injuries), while OPEN injuries were more diverse. Use of ENDO for NCTH increased from 23% in 2008 to 39% in 2012. After adjusting for age, mechanism, ISS, use of REBOA, and admission SBP, base excess, and platelet count, multivariate logistic regression found that ENDO was associated with decreased mortality compared to OPEN (OR 0.38, 95% CI 0.19 – 0.77).

Conclusion: ENDO was used in a relatively narrow range of bleeding control indications in this NCTH population. Although ENDO may reduce mortality in NCTH patients, significant group differences limit the generalizability of this finding.

Introduction

Hemorrhage is the leading cause of potentially preventable civilian[1,2] and military[3] trauma deaths. In contrast to other causes of trauma death, such as traumatic brain injury (TBI), sepsis, and multiple organ failure, exsanguination occurs rapidly (median 2-3 hours after presentation).[4,5] Although great progress has been made in the rapid control of compressible hemorrhage (especially use of tourniquets to stop extremity hemorrhage),[6,7,8] initial management of non-compressible torso hemorrhage (NCTH) from intra-thoracic and intra-abdominal sources is still a significant challenge.[8,9] A retrospective review of 4,596 combat casualties from 2001 – 2011 in Afghanistan and Iraq found that 24% of deaths were potentially preventable and substantially related to hemorrhage control. Of the potentially preventable deaths, 67% were due to NCTH.[8] An epidemiologic study of the National Trauma Data Bank found that NCTH was associated with nearly 50% mortality in civilian trauma patients.[9]

Until recently, open thoracotomy and/or laparotomy were the only options for definitive control of NCTH. The advent of endovascular techniques has opened the possibility of using this minimally invasive approach for definitive control of NCTH. However, both precise anatomic description of the source of NCTH and comparisons of endovascular versus open techniques for control of NCTH are lacking in the literature. The objective of this study was therefore two-fold: first, to describe the precise anatomic locations of bleeding in a population of trauma patients with NCTH, and second, to compare an endovascular (ENDO) versus open (OPEN) approach for definitive control of NCTH.

Methods:

Study design

Approval was obtained from the institutional review boards of all four study sites: the University of Texas Health Science Center at Houston (UTHealth), Baylor College of Medicine, the University of Texas Health Science Center at San Antonio, and the San Antonio Military Medical Center as well as the Human Research Protections Office of the US Army Medical Research and Materiel Command. Each institutional trauma registry was queried to identify trauma patients who presented between 2008–2012 with NCTH defined as 1) named axial torso vessel disruption, 2) Abbreviated Injury Scale (AIS) chest or abdomen ≥3 with concomitant shock (base deficit >4) or emergent operation (≤90 minutes after presentation), or 3) pelvic fracture with ring disruption. Patients who had an isolated hip fracture or isolated fall from standing were excluded. Demographic information including age, sex, mechanism of injury, Glasgow Coma Score (GCS), admission vital signs, admission laboratory studies, Abreviated Injury Scale (AIS) and Injury Severity Score (ISS), transfusion of blood products, use of resuscitative endovascular balloon occlusion of the aorta (REBOA), ICU-free days, and mortality were obtained from the medical record. Radiological and/or operative reports were reviewed to describe as specifically as possible the anatomic location of NCTH or the specific vessel injured. Patients were divided into ENDO and OPEN groups depending on the initial approach for control of NCTH. Those who did not undergo an ENDO or OPEN procedure for definitive NCTH control were excluded from the primary analysis. Study data were collected and managed at UTHealth using REDCap (Research Electronic Data Capture),[10] a secure, web-based application designed to support data capture for research studies.

Statistical analysis

Statistical analysis was performed using Stata 14.1 (StataCorp LP, College Station, TX). Data are reported as median values with interquartile range (IQR) or proportions as appropriate. Categorical data were analyzed by Chi-square test. Nonparametric comparisons of continuous variables were performed using the Wilcoxon rank-sum test. A purposeful multiple logistic regression model was constructed to test the hypothesis that ENDO was associated with decreased in-hospital mortality. Covariates were chosen if they were significant at the $p<0.20$ level on univariate analysis or thought to potentially affect the outcome of mortality. This set of covariates was then iteratively reduced, removing covariates which were non-significant at the $p<0.10$ level and not confounders in the multiple logistic regression model, as described by Bursac et al.[11] Beside covariate selection as described above, a two-tailed significance level of $\alpha < 0.05$ was used for all statistical tests.

Results

During the study period, 678 patients with NCTH presented to the four centers. Forty patients (6%) were excluded due to missing definitive hemorrhage control data. Seventy-eight patients (12%) did not undergo any intervention for definitive control of NCTH. Of these, 30 patients (38%) died with median time to death of 2 hours and interquartile range (IQR) of 1 to 7 hours. For the 25 patients in this group who had cause of death information available, exsanguination accounted for the majority of deaths (n=19; 76%), which included 14 patients where initial hemorrhage control was attempted with REBOA. The anatomic location of NCTH for patients who did not undergo definitive NCTH control is listed in Table 1.

Five hundred and sixty patients (83%) underwent either an ENDO (n=175, 31%) or OPEN (n=385, 69%) procedure for initial definitive control of NCTH. Use of ENDO for NCTH increased from 23% in 2008 to 39% in 2012. Patients in the ENDO group were older (median 38 vs 31 years), less likely to be male (74% vs 83%), more likely victims of blunt trauma (95% vs 32%), and had lower platelet count on admission (median 228 vs 213 x 10^9/L) (all $p<0.05$, Table 2). Admission vital signs including Glasgow Coma Score (GCS) and admission hemoglobin were similar ($p>0.05$). Although ENDO patients had lesser admission base deficit than OPEN patients (median 7 vs 8 mEq/L, $p<0.01$), the incidence of shock defined as base deficit >4 was similar (70% vs 70%, $p=0.97$). ENDO patients had significantly increased AIS scores for the head, chest, and extremities (all $p<0.001$), which translated into a significantly higher ISS compared to OPEN patients (median 34 vs 25, $p<0.001$). However, ENDO patients had statistically decreased AIS abdomen scores ($p<0.01$) due to a lower proportion of patients with AIS abdomen ≥4 (31% vs 48%) despite having the same median of 3 and IQR (3 to 4) as OPEN patients. Time to intervention was significantly longer in the ENDO group compared to the OPEN group (median 295 vs 87 minutes, $p<0.001$).

Patients in the ENDO group underwent intervention for a narrow range of vascular injuries (Table 3). Two sources of injury, internal iliac arteries and branches (n=76, 43%) and the descending aorta (n=44, 25%), accounted for over half of all ENDO procedures. ENDO interventions of the intra-abdominal arteries (n=23, 13%) and the renal arteries (n=14, 8%) were also relatively common. Partial transection or flow limiting defect (n=68, 39%) and pseudoaneurysm (n=55, 31.4%) accounted for most ENDO arterial injuries (Table 4). Specific procedures performed were placement of covered stent-graft (n=40, 23%), placement of bare-metal stent (n=17, 10%), and embolization (n=108, 62%). All but 5 ENDO procedures were performed for arterial bleeding (Table 5).

In contrast, OPEN procedures were performed for a wide range of NCTH sources (Table 3) including 147 interventions (38%) on venous hemorrhage without concomitant arterial injury (Table 5). Arterial injuries in the OPEN group were most commonly complete transections (n=126, 33%) and partial transections (n=69, 18%) (Table 4). Several relatively common indications of OPEN intervention, such as injury to the intercostal/internal mammary arteries (n=19, 5%), the inferior vena cava (n=56, 5%), superior mesenteric artery (n=19, 5%), and abdominal visceral veins including the portal vein (n=33, 9%), had no representation in the ENDO group. Specific OPEN procedures performed were ligation of bleeding vessel (n=171, 44%), temporary stent placement (n=11, 3%), primary repair (n=208, 54%), repair with vein interposition or bypass graft (n=7, 2%), and repair with synthetic graft (n=20, 5%) with multiple modalities used in some patients.

Patients in the ENDO group received fewer RBC units within the first 24 hours (median 5 vs 9 units, $p<0.01$) but were transfused similar amounts of plasma (median 6 vs 5 units, $p=0.88$) and platelets (6 vs 6 units, $p>0.53$). On univariate analysis, patients in the ENDO group had significantly less mortality than OPEN patients (17% vs 31%, $p<0.001$). Whereas the most common cause of death in the ENDO group was multiple organ failure (52%) with median time to death of 32 hours, the vast majority of OPEN patients exsanguinated (72%) with median time to death of 3 hours. ICU-free days (median 18 vs 17 days, $p=0.49$) and incidence of rebleeding requiring an additional unplanned endovascular or open procedure (5% vs 3%, $p=0.43$) were also similar between groups. After construction of a purposeful multivariable logistic regression model which included the study site, age, mechanism, ISS, use of REBOA, and admission SBP, base excess, and platelet count as covariates, use of ENDO was significantly associated with reduced risk of mortality compared to OPEN (odds ratio [OR] 0.38, 95% confidence interval [CI] 0.19 – 0.77).

Discussion

We performed a retrospective study of adult patients presenting to four level 1 trauma centers with NCTH from 2008 to 2012. These centers collectively represent all of the level 1 centers in the Houston and San Antonio metropolitan areas; this study is therefore population-based and includes all patients who sustained NCTH during the study period and survived to hospital presentation. The most common cause of death of all patients in this study was exsanguination (75%): median time to exsanguination was 2 hours, consistent with other studies of hemorrhaging trauma patients,[4,5] and a testament to the time criticality of hemorrhage control. After adjusting for baseline covariates including study site, age, mechanism, ISS, use of REBOA, and admission SBP, base excess, and platelet count, multivariable logistic regression analysis found that ENDO was significantly associated with decreased mortality compared to OPEN in all patients (OR 0.38, 95% CI 0.19 – 0.77).

Given the ubiquity of endovascular therapy in the elective treatment of vascular disease and its successful use in vascular emergencies such as ruptured abdominal aortic aneurysm repair,[12] definitive endovascular treatment of traumatic hemorrhage is an increasingly viable option.[13] The advantages of an endovascular versus open approach are related to its minimal invasiveness: decreased intra-procedure physiologic stress and insensible fluid losses, decreased wound complications, and faster patient recovery. One of the first areas where endovascular technique was identified as a viable modality for traumatic hemorrhage control was bleeding from pelvic fractures,[14] which can be substantial and difficult to control by laparotomy or preperitoneal packing.[15] The open approach to pelvic hemorrhage control may exacerbate venous hemorrhage by disruption of the hematoma, which is avoided in the endovascular approach. Current guidelines from the Eastern Association for the Surgery of Trauma (EAST) recommend pursuing endovascular management for any hemodynamically unstable patient with hemorrhage related to pelvic fractures without significant bleeding from another source

(Level I recommendation), while preperitoneal packing is recommended as a salvage therapy when endovascular embolization has failed (Level III recommendation).[16] EAST guidelines also "strongly" recommend endovascular therapy as first-line treatment for blunt traumatic aortic injury owing to its minimal invasiveness and increased provider experience with endovascular versus open aortic repair.[17] However, EAST guidelines recommend endovascular treatment for select (hemodynamically stable) patients with bleeding secondary to blunt hepatic[18] or splenic[19] injuries (Level II recommendation), whereas hemodynamically unstable patients or those with diffuse peritonitis should undergo open exploration (Level I).

ENDO and OPEN patients had significant between-group disparities. ENDO patients had significantly decreased admission base deficit (median 7 vs 8 mEq/L, $p<0.01$) and significantly less frequent use of REBOA (3% vs 16%, $p<0.001$), suggesting that OPEN patients had experienced increased blood loss prior to admission. Patients in the ENDO group had substantially higher ISS (median 34 vs 25) than OPEN patients. Despite statistical significance, differences in AIS chest and abdomen were small, and the ISS difference is largely explained by differences in the AIS extremity score (median 3 vs 0) and, to a lesser degree, in the AIS head score (Table 2). Injury severity differences are likely due to the substantial disparity in injury mechanism: whereas 95% of ENDO patients suffered blunt injury, only 32% of OPEN patients had sustained blunt trauma. Patients who had sustained penetrating thoracoabdominal injury likely had greater incidence of open exploration for management of concomitant injury (e.g. bowel injury), although these data were not captured for this study.

Another key difference between ENDO and OPEN patients was anatomic location of NCTH (Table 8). The single most common anatomic location of intervention in the ENDO group was bleeding from the internal iliac arteries and branches (n=73, 42%), which was uncommon in the OPEN group (n=34, 9%). In patients with iliac artery hemorrhage (n=107, 19%), rate of mortality was consistent with another

recently published report[20] and was interestingly no different between ENDO and OPEN patients (25% vs 24%, p=0.90). Interventions on the thoracic aorta was the next most common area of intervention in ENDO patients (n=47, 27%), which was also uncommon in OPEN patients (n=28, 7%). Current data suggests that delayed (>24 hours) repair of blunt thoracic aortic injury is safe.[17] Indeed, ENDO patients with thoracic aortic injury were overwhelmingly victims of blunt trauma (n=46, 98%), had delayed time to intervention (median 840 minutes) even compared to ENDO patients as a whole (median 295 minutes), and had low mortality (n=2, 4%). Conversely, OPEN patients with thoracic aortic injury had less blunt injury (n=16, 57%) decreased time to intervention (median 78 minutes), and higher mortality (n=13, 46%) predominantly due to exsanguination (n=10, 77%). ENDO patients had significantly decreased admission base deficit compared to OPEN patients (median 5 vs 10 mEq/L, p<0.01), suggesting that OPEN patients had experienced more blood loss at the time of admission. Notably, REBOA was used in 12 patients (1 in ENDO and 11 in OPEN) with thoracic aortic injury. The circumstances of REBOA use were not available for this study, and it is unclear if this contributed to the high (46%) mortality in OPEN patients with thoracic aortic injury. Intra-abdominal arterial hemorrhage was the third most common indication for intervention in ENDO patients (n=23, 13%) and the most common indication for arterial intervention in OPEN patients (n=78, 20%). ENDO patients had a trend toward higher admission SBP (median 124 vs 97 mmHg, p=0.05) and decreased mortality (13% vs 33%, p=0.06), as well as significantly longer time to death (median 29 vs 4 hours, p=0.04), consistent with current guidelines which recommend endovascular treatment of intra-abdominal hemorrhage in only select (hemodynamically stable) patients, while those with hemodynamic instability or diffuse peritonitis should undergo open exploration.[18,19] Interestingly, OPEN patients in this category had increased time to intervention (median 115 minutes) compared to OPEN patients overall (median 87 minutes).

. One limitation of this study is that indicators of response to initial resuscitation, such as number of blood products transfused within the first few hours after admission, presence of computed

tomography (CT) scan prior to definitive hemorrhage control, and perioperative vital signs or laboratory data, were not available. These data could have been used to identify patients with hyperacute hemorrhage, in whom OPEN intervention is clearly indicated, and a non-hyperacute hemorrhage group, in whom ENDO or OPEN treatment may be reasonable. Even though ENDO and OPEN patients had no difference in incidence of shock (70% vs 70%, p=0.97) and hypotension (30% vs 32%, p=0.56) at admission, the substantial disparity in time to intervention (median 295 vs 87 minutes), time to death (32 vs 3 hours), and incidence of exsanguination (45% vs 72%) (all $p<0.001$) all suggest that most ENDO patients were relatively stable after initial resuscitation and that more OPEN patients had hyperacute hemorrhage.

In conclusion, use of endovascular techniques for non-elective indications is increasing. In this study of trauma patients presenting with NCTH, endovascular treatment was used in a narrow range of vascular injuries after predominantly blunt mechanism and in a much more delayed fashion compared to open hemorrhage control. Although endovascular treatment in this study was significantly associated with decreased mortality in all patients, significant group differences between ENDO and OPEN groups limit the generalizability of this finding.

Acknowledgments

Non-Compressible Torso Hemorrhage (NCTH) Study Group:
Clinical Coordinating Center: John B. Holcomb, MD; Charles E. Wade, PhD; Erin E. Fox, PhD; Jeanette M. Podbielski, RN. Jeffrey S. Tomasek, MD.
Data Coordinating Center: Stacia M. DeSantis, PhD; Thomas J. Greene, MPH.
Delphi Meeting Attendees: Charlton-Ouw, MD; O. Clark West, MD ; Martin A. Schreiber, MD; Lena Napolitano, MD; Frederic Pieracci, MD; Charles Fox, MD; Steven Shackelford, MD; Matthew Martin, MD; Joseph J. DuBose, MD; Todd Rasmussen, MD; Megan Brenner, MD; Laura L. Moore, MD; C Rodriquez, MD

NCTH Clinical Sites (listed in order of number of patients enrolled):
University of Texas Health Science Center at Houston: Garrett Jost, Gerald R. Fortuna, Jr., MD.

University of Texas Health Science Center at San Antonio: Brian J. Eastridge, MD; Rachelle Babbitt-Jonas; Jessica Raley
Baylor College of Medicine: Ramyar Gilani, MD; Samuel R. Todd, MD; Reginya Knight
U.S. Army Institute of Surgical Research: Jennifer Gurney, MD; Valerie G. Sams, MD; Kevin K. Chung, MD; Sonya Charo-Griego

Table 1. NCTH locations of patients not undergoing ENDO or OPEN (n=78)

	Survivors (n=48, 62%)			Non-survivors (n=30, 38%)	
Pulmonary artery	0	0.0%		1	3.3%
Ascending aorta	1	2.1%		5	16.7%
Aortic arch	4	8.3%		2	6.7%
Intra-thoracic common carotid artery	6	12.5%		0	0.0%
Subclavian artery	4	8.3%		0	0.0%
Intercostal arteries	2	4.2%		0	0.0%
Descending thoracic aorta	10	20.8%		7	23.3%
Abdominal aorta	1	2.1%		2	6.7%
Celiac artery	1	2.1%		0	0.0%
Renal artery	6	12.5%		0	0.0%
Infra-renal aorta	2	4.2%		0	0.0%
Common iliac arteries	0	0.0%		1	3.3%
External iliac arteries	1	2.1%		1	3.3%
Internal iliac arteries	3	6.3%		2	6.7%
Superior vena cava	0	0.0%		1	3.3%
Subclavian vein	1	2.1%		0	0.0%
Innominate vein	1	2.1%		0	0.0%
Retro-hepatic inferior vena cava	1	2.1%		2	6.7%
Portal vein	1	2.1%		0	0.0%
Supra-renal/Sub-hepatic inferior vena cava	0	0.0%		1	3.3%
Infra-renal inferior vena cava	1	2.1%		0	0.0%
External iliac vein	1	2.1%		0	0.0%
Unknown	1	2.1%		3	10.0%

Table 2. Demographics of ENDO and OPEN groups

Variable	ENDO (n=175, 31%)	OPEN (n=385, 69%)	p
Age	38 (24, 54)	31 (23,42)	<0.001
Male	130 (74%)	318 (83%)	0.02
Blunt	166 (95%)	125 (32%)	<0.001
AIS head	0 (0, 3)	0 (0, 0)	<0.001
AIS chest	3 (2, 4)	3 (0, 4)	<0.001
AIS abd	3 (3, 4)	3 (3, 4)	<0.01
AIS extrem	3 (2, 3)	0 (0, 2)	<0.001
ISS	34 (24, 41)	25 (16, 34)	<0.001
ED SBP	107 (85, 127)	100 (80, 125)	0.11
ED hyptension (SBP<90 mmHg)	52 (30%)	124 (32%)	0.56
ED HR	109 (88, 129)	103 (82, 127)	0.08
ED GCS	14 (3, 15)	14 (3, 15)	0.32
ED Hgb	11.8 (10.4, 13.3)	11.9 (10.2, 13.2)	0.58
ED Plt	228 (174, 289)	213 (145, 273)	0.01
ED Base deficit	7 (4, 11)	8 (4, 14)	<0.01
ED Shock (BD> 4 mEq/L)	123 (70%)	270 (70%)	0.97
ED REBOA	5 (3%)	61 (16%)	<0.001
Time to intervention (min)	295 (190, 677)	87 (58, 144)	<0.001

Table 3. Arterial injuries (with or without concomitant venous injury)

	ENDO (n=175, 31%)			OPEN (n=385, 69%)	
Pulmonary artery				7	1.8%
Ascending aorta	1	0.6%		10	2.6%
Aortic arch	2	1.1%		2	0.5%
Innominate artery				2	0.5%
Subclavian artery (Right)	2	1.1%		8	2.1%
Intra-thoracic right common carotid artery				2	0.5%
Intra-thoracic left common carotid artery				3	0.8%
Subclavian artery (Left)	2	1.1%		6	1.6%
Intercostal arteries				19	4.9%
Descending thoracic aorta	44	25.1%		16	4.2%
Abdominal aorta	1	0.6%		9	2.3%
Visceral abdominal aorta				2	0.5%
Celiac artery				3	0.8%
Common hepatic artery	8	4.6%		10	2.6%
L hepatic artery	2	1.1%		1	0.3%
R hepatic artery	5	2.9%		1	0.3%
Splenic artery	6	3.4%		6	1.6%
Left gastric artery	1	0.6%		3	0.8%
Gastroepiploic artery				3	0.8%
Superior mesenteric artery				21	5.5%
Ileocolic artery				1	0.3%
Inferior mesenteric artery				3	0.8%
Other abdominal visceral arteries				15	3.9%
Renal artery	14	8.0%		10	2.6%
Infra-renal aorta	1	0.6%		6	1.6%
Common iliac arteries	1	0.6%		9	2.3%
External iliac arteries	4	2.3%		15	3.9%
Internal iliac arteries	54	30.9%		21	5.5%
Internal iliac artery branches	19	10.9%		13	3.4%
Total	167	95.4%		227	59.0%

Table 4. Type of arterial injury

	ENDO (n=175, 31%)			OPEN (n=385, 69%)	
Transection	27	15.4%		126	32.7%
Complete occlusion	7	4.0%		1	0.3%
Partial transection or flow limiting defect (e.g. intimal flap, dissection)	68	38.9%		69	17.9%
Pseudoaneurysm	55	31.4%		16	4.2%
Other	6	3.4%		6	1.6%
Unknown	7	4.0%		16	4.2%
Total	170	97.1%		234	60.8%

Table 5. Venous injuries (without concomitant arterial injury)

	ENDO (n=175, 31%)			OPEN (n=385, 69%)	
Pulmonary vein				4	1.0%
Superior vena cava				4	1.0%
Innominate vein				3	0.8%
Subclavian vein				7	1.8%
Suprarenal/Subhepatic inferior vena cava				21	5.5%
Retro-hepatic inferior vena cava				9	2.3%
Portal vein	1	0.6%		7	1.8%
Splenic vein				10	2.6%
Superior mesenteric vein				12	3.1%
Renal vein				8	2.1%
Gonadal vein	1	0.6%		4	1.0%
Infra-renal inferior vena cava				20	5.2%
Inferior vena cava, unspecified				6	1.6%
Common iliac veins				18	4.7%
External iliac vein				11	2.9%
Internal iliac vein	3	1.7%		3	0.8%
Total	5	2.9%		147	38.2%

Table 6. Type of venous injury

	ENDO (n=175, 31%)			OPEN (n=385, 69%)	
Transection	1	0.6%		81	21.0%
Partial transection	1	0.6%		50	13.0%
Other	2	1.1%		5	1.3%
Unknown	1	0.6%		12	3.1%
Total	5	2.9%		148	38.4%

Table 7. Outcomes of ENDO vs OPEN groups

Variable	ENDO (n=175, 31%)	OPEN (n=385, 69%)	P
24h RBC (units)	5 (1, 11)	9 (3, 18)	<0.01
24h Plasma (units)	6 (1, 15)	5 (2, 14)	0.88
24h Plt (units)	6 (0, 12)	6 (0, 12)	0.53
24h Plasma:RBC ratio	0.84 (0.25, 1.13)	0.62 (0.17, 0.97)	<0.01
24h Plt:RBC ratio	0.5 (0, 1)	0.14 (0, 0.71)	0.12
Rebleeding	9 (5%)	13 (3%)	0.43
ICU-free days	18 (2, 25)	17 (0, 27)	0.49
Death	29 (17%)	120 (31%)	<0.001
Time to death (hours)	32 (7, 157)	3 (2, 9)	<0.001
Causes of death (not mutually exclusive)			
Exsanguination	13 (45%)	87 (72%)	<0.001
TBI	9 (31%)	6 (5%)	<0.001
Respiratory	2 (7%)	3 (3%)	0.27
Sepsis	3 (10%)	6 (5%)	0.32
Multiple organ failure	15 (52%)	8 (7%)	0.06
Myocardial infarction	1 (3%)	2 (2%)	0.50
Stroke	1 (3%)	3 (3%)	1.00
Pulmonary embolism	1 (3%)	0 (0%)	0.05

Table 8. ENDO vs OPEN for most common anatomic locations of ENDO intervention

	Internal iliac artery hemorrhage			Thoracic aorta injury			Intra-abdominal arterial hemorrhage		
	ENDO (n=73, 42%)	OPEN (n=34, 9%)	p	ENDO (n=47, 27%)	OPEN (n=28, 7%)	p	ENDO (n=23, 13%)	OPEN (n=78, 20%)	p
Age	38 (27, 57)	34 (23, 50)	0.31	38 (21, 53)	29 (21, 37)	0.19	43 (31, 54)	33 (25, 48)	0.07
Blunt	72 (99%)	15 (44%)	<0.001	46 (98%)	16 (57%)	<0.001	22 (96%)	36 (46%)	<0.001
ISS	29 (22, 41)	22 (11, 34)	<0.01	34 (25, 41)	34 (26, 49)	0.33	38 (34, 45)	25 (17, 34)	<0.001
ED SBP	102 (80, 118)	96 (76, 123)	0.90	109 (92, 130)	97 (81, 127)	0.10	124 (84, 140)	97 (77, 130)	0.05
ED base deficit	8 (5, 11)	6 (4, 11)	0.62	5 (4, 10)	10 (6, 18)	<0.001	7 (5, 13)	9 (3, 15)	0.75
ED REBOA	3 (4%)	3 (9%)	0.32	1 (2%)	11 (39%)	<0.001	1 (4%)	9 (12%)	0.31
Time to intervention (minutes)	261 (184, 506)	95 (74, 132)	<0.001	840 (530, 2876)	78 (59, 555)	<0.001	290 (158, 415)	115 (78, 215)	<0.001
24h RBC	8 (5, 16)	12 (4, 24)	0.49	3 (2, 10)	8 (4, 16)	<0.01	8 (2, 12)	14 (7, 22)	0.02
24h plasma	7 (3, 17)	8 (3, 18)	0.68	3 (0, 6)	4 (2, 9)	0.15	6 (4, 14)	8 (4, 17)	0.57
24h platelets	6 (0, 18)	6 (0, 18)	0.79	0 (0, 6)	0 (0, 3)	0.52	6 (0, 12)	6 (0, 12)	0.51
Rebleed	3 (4%)	1 (3%)	0.77	0 (0%)	2 (7%)	0.10	3 (13%)	3 (4%)	0.10
Mortality	18 (25%)	8 (24%)	0.90	2 (4%)	13 (46%)	<0.001	3 (13%)	26 (33%)	0.06
Time to Death (hours)	49 (6, 157)	6 (2, 35)	0.03	117 (20, 213)	2 (1, 5)	0.08	29 (9, 788)	4 (2, 8)	0.04
Causes of Death*			<0.01			<0.01			<0.01
Exsanguination	8 (44%)	5 (63%)		0 (0%)	10 (77%)		1 (33%)	17 (65%)	
TBI	5 (28%)	1 (13%)		1 (50%)	0 (0%)		2 (67%)	1 (4%)	
Respiratory	1 (6%)	0		1 (50%)	0 (0%)		0	0 (0%)	
Sepsis/MOF	8 (44%)	2 (25%)		0 (0%)	3 (23%)		0	7 (27%)	
MI/Stroke	2 (11%)	0		0 (0%)	0 (0%)		0	2 (8%)	
PE	0	0		0 (0%)	0 (0%)		0	0	

* not mutually exclusive

References:

1. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma*. 1995;38(2):185-193.

2. Tien HC, Spencer F, Tremblay LN, et al. Preventable deaths from hemorrhage at a level I Canadian trauma center. *J Trauma*. 2007;62(1):142-146.

3. Kotwal RS, Montgomery HR, Kotwal BM, et al. Eliminating Preventable Death on the Battlefield. *Arch Surg*. 2011;146(12):1350-1358.

4. Holcomb JB, del Junco DJ, Fox EE, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg 2013;148:127-136.

5. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015;313:471-482.

6. Kragh JF Jr, Littrel ML, Jones JA, et al. Battle casualty survival with emergency tourniquet use to stop limb bleeding. *J Emerg Med*. 2011;41(6):590-597.

7. Kragh JF Jr, Walters TJ, Baer DG, et al. Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Ann Surg*. 2009;249(1):1-7.

8. Eastridge BJ, Mabry RL, Seguin P, et al. Death on the battlefield (2001-2011): implications for the future of combat casualty care. J Trauma Acute Care Surg. 2012;73(6 Suppl 5):S431-S437.

9. Kisat M, Morrison JJ, Hashmi ZG, et al. Epidemiology and outcomes of non-compressible torso hemorrhage. *J Surg Res*. 2013;184(1):414-421.

10. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.

11. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. 2008;3:17.

12. Ullery BW, Tran K, Chandra V, et al. Association of an Endovascular-First Protocol for Ruptured Abdominal Aortic Aneurysms With Survival and Discharge Disposition. *JAMA Surg*. 2015;150(11):1058-1065.

13. Reuben BC, Whitten MG, Sarfati M, Kraiss LW. Increasing use of endovascular therapy in acute arterial injuries: Analysis of the National Trauma Data Bank. *J Vasc Surg.* 2007;46(6):1222-1226.

14. Agolini SF, Shah K, Jaffe J, et al. Arterial embolization is a rapid and effective technique for controlling pelvic fracture hemorrhage. *J Trauma*. 1997;43(3):395-399.

15. Panetta T, Sclafani SJ, Goldstein AS, et al. Percutaneous transcatheter embolization for massive bleeding from pelvic fractures. *J Trauma.* 1985;25(11):1021.

16. Cullinane DC, Schiller HJ, Zielinski MD, et al. Eastern Association for the Surgery of Trauma practice management guidelines for hemorrhage in pelvic fracture--update and systematic review. *J Trauma*. 2011;71(6):1850-1868.

17. Fox N, Schwartz D, Salazar JH, et al. Evaluation and management of blunt traumatic aortic injury: A practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg.* 2015;78(1):136-146.

18. Stassen NA, Bhullar I, Cheng JD, et al. Nonoperative management of blunt hepatic injury: An Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*. 2012;73(5):S288-S293.

19. Stassen NA, Bhullar I, Cheng JD, et al. Selective nonoperative management of blunt splenic injury: An Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*. 2012;73(5):S294-S300.

20. Lindahl J, Handolin L, Söderlund T, Porras M, Hirvensalo E. Angiographic embolization in the treatment of arterial pelvic hemorrhage: evaluation of prognostic mortality-related factors. *Eur J Trauma Emerg Surg*. 2013 Feb;39(1):57-63.

Appendix 3. IRB/HRPO documents from Y2 for the prospective study

UTHealth
The University of Texas
Health Science Center at Houston

Committee for the Protection of Human Subjects
6410 Fannin Street, Suite 1100
Houston, Texas 77030

Dr. John Holcomb
UT-H - MS - Surgery

NOTICE OF APPROVAL TO BEGIN RESEARCH **July 20, 2016**

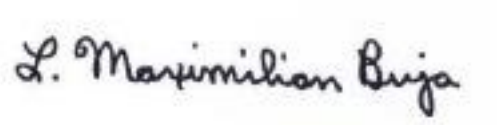
HSC-GEN-16-0501 - Hemorrhage Control for Major Traumatic Vascular InjuriesPhase II: A Prospective Observational Study of Non-Compressible Torso Hemorrhage(NCTH)

Number of Subjects Approved: Target: 300 **/Screen:** 300

PROVISIONS: This approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consent, etc.

APPROVED: At a Convened Meeting on 06/24/2016

EXPIRATION DATE: 05/31/2017

CHAIRPERSON: L. Maximilian Buja, MD 

Subject to any provisions noted above, you may now begin this research.

CHANGES: The principal investigator (PI) must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.

INFORMED CONSENT DETERMINATION:
Waiver of Consent Granted

INFORMED CONSENT: Informed consent must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. Please note that only copies of the stamped approved informed consent form can be used when obtaining consent.

HEALTH INSURANCE PORTABILTY AND ACCOUNTABILITY ACT (HIPAA):

Waiver of HIPAA Authorization granted:
Information to be accessed: Medical Record Number, date of birth, date of admission, date of discharge, name.
Information to be retained: Medical Record Number, date of birth, date of admission, date of discharge, name.

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS: The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

RECORDS: The PI will maintain adequate records, including signed consent documents if required, in a manner that ensures subject confidentiality.

UTHealth
The University of Texas
Health Science Center at Houston

Committee for the Protection of Human Subjects
6410 Fannin Street, Suite 1100
Houston, Texas 77030

NOTICE OF APPROVAL TO IMPLEMENT REQUESTED CHANGES

September 12, 2016

HSC-GEN-16-0501 - Hemorrhage Control for Major Traumatic Vascular Injuries Phase II: A Prospective Observational Study of Non-Compressible Torso Hemorrhage(NCTH)
PI: John Holcomb, MD, FACS

Reference Number: 142253

PROVISIONS; Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consent, etc.

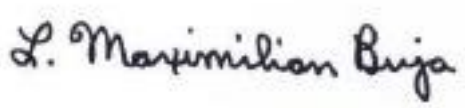
APPROVED: By Expedited Review and Approval

CHANGE APPROVED: Reciprocity Agreement with University of Texas San Antonio
PI: San Antonio Site – Brian J.Eastridge

REVIEW DATE: September 12, 216

APPROVAL DATE: September 12, 2016

CHAIRPERSON: L. Maximilian Buja, MD



Upon receipt of this letter, and subject to any provisions noted above, you may now implement the changes approved.

CHANGES: The principal investigator (PI) must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.

INFORMED CONSENT: Informed consent must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. **Please note that if revisions to the informed consent form were made and approved, then old blank copies of the ICF MUST be destroyed. Only copies of the appropriately dated, stamped approved informed consent form can be used when obtaining consent.**

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS: The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

RECORDS: The PI will maintain adequate records, including signed consent documents if required, in a manner that ensures subject confidentiality.

Harris Health System
P.O. Box 66769, Houston, Texas 77266-6769

09/21/2016

Ramyar Gilani

eProtocol Number:16-09-1478

Re: H-39639: Hemorrhage Control for Major Traumatic Vascular Injuries Phase II: A Prospective Observational Study of Non-Compressible Torso Hemorrhage (NCTH)

Location: Ben Taub Hospital

NOTICE OF APPROVAL FOR HUMAN RESEARCH

APPROVAL VALID FROM 09/21/2016 TO 08/17/2017

Harris Health System is pleased to inform you that the protocol named above has been approved for implementation. The study may not continue after the approval period without additional IRB and Harris Health System review and approval. It is your responsibility to assure the study is not conducted beyond the expiration date.

The Principal Investigator must receive approval from the IRB and Harris Health System before initiating any changes, including those required by the Sponsor, which would affect human subjects (e.g. changes in methods or procedures, numbers or kinds of human subjects or revisions to the informed consent document or procedures).

Please be aware that only copies of the appropriately dated, stamped IRB- and Harris Health System-approved informed consent documents can be used when written informed consent is required. You must discard all previous informed consent documents being used and replace them with the stamped, validated version.

The Harris Health System must be acknowledged in all publications and the logo included on all platform and poster presentations for research conducted within the system. Copies of platform presentations, poster presentations, and publications of research performed at the Harris Health System should be provided to the Harris Health System Research & Sponsored Programs department.

Sincerely,

Julie Thompson, Ph.D.

Administrative Director, Research and Sponsored Programs

Harris Health System

From:	Podbielski, Jeanette M
To:	Holcomb, John B; Wade, Charles E; Fox, Erin E; Tomasek, Jeffrey S; Greene, Thomas J; DeSantis, Stacia M; Haymaker, Amanda
Subject:	FW: A-18067.2a and A-18067.2b HRPO Approval Memorandum (Proposal Log Number 13057176, Award Number W81XWH-14-1-0112)
Date:	Wednesday, October 05, 2016 2:43:53 PM

To all,
We have received HRPO approval for the prospective NCTH study for us and UTSA. For our site, we are waiting for the DUA to be signed off between MH and UT and then will need to wait for MH approval before we can begin.
Thanks,
Jeanette

From: Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US) [mailto:kimberly.l.odam.civ@mail.mil]
Sent: Wednesday, October 05, 2016 2:26 PM
To: Holcomb, John B; 'eastridge@uthscsa.edu'
Cc: Toups, Krystal R; Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Doan, Robert T Jr CIV USARMY MEDCOM USAMRAA (US); Jorgensen, Shelley C CIV USARMY MEDCOM CDMRP (US); Brosch, Laura R CIV USARMY MEDCOM USAMRMC (US); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US); Bowden, Derek T CTR USARMY MEDCOM USAMRMC (US); Podbielski, Jeanette M; Soto, Joseph D CTR USARMY MEDCOM USAMRMC (US)
Subject: A-18067.2a and A-18067.2b HRPO Approval Memorandum (Proposal Log Number 13057176, Award Number W81XWH-14-1-0112)

SUBJECT: Initial Approval for the Protocol, "Hemorrhage Control for Major Traumatic Vascular Injuries Phase II: A Prospective Observational Study of Non-Compressible Torso Hemorrhage (NCTH)," Submitted by John B. Holcomb, MD, University of Texas Health Science Center, Houston, Texas (HRPO Log Number A-18067.2a), and Brian J. Eastridge, MD, University of Texas Health Science Center, San Antonio, Texas (HRPO Log Number A-18067.2b), in Support of the Proposal, "Hemorrhage Control for Major Traumatic Vascular Injuries," Submitted by John B. Holcomb, MD, University of Texas Health Science Center, Houston, Texas, Proposal Log Number 13057176, Award Number W81XWH-14-1-0112, HRPO Log Numbers A-18067.2a (University of Texas Health Science Center, Houston Site) and A-18067.2b (University of Texas Health Science Center, San Antonio Site)

1. The subject protocol (version 1.0/date 24 May 2016) was approved by the University of Texas Health Science Center (UTHSC) at Houston Institutional Review Board (IRB) on 24 June 2016. The UTHSC at San Antonio is relying on the review provided by the UTHSC at Houston IRB through a reciprocity agreement approved 12 September 2016. The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, US Army, and USAMRMC human subjects protection requirements.

2. This no greater than minimal risk study is approved for the enrollment of 300 subjects across UTHSC Houston and San Antonio.

3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRMC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.

4. The Principal Investigator must provide the following post-approval submissions to the HRPO via email to Usarmy.detrick.medcom-usamrmc.other.hrpo-cr-documents@mail.mil. Failure to comply could result in suspension of funding.

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change in the IRB of Record, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the IRB is due no later than 31 May 2017. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) or mail to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other

government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

5. Please note: The USAMRMC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

6. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.

7. The HRPO point of contact for this approval is Derek Bowden, MA, Human Subjects Protection Scientist, at 301-619-1667/derek.t.bowden2.ctr@mail.mil.

8. The HRPO point of contact for post-approval oversight is Joseph Soto, Human Subjects Protection Scientist, at extension 301-619-3098/joseph.d.soto.ctr@mail.mil.

KIMBERLY L. ODAM, MS, CIP
Deputy Director
Human Research Protection Office
Office of Research Protections
US Army Medical Research and Materiel Command

Note: The official copy of this memo is housed with the protocol file at the Office of Research Protections, Human Research Protection Office, 810 Schreider Street, Fort Detrick, MD 21702-5000. Signed copies will be provided upon request.

Appendix 4. Protocol and Manual of Operations for prospective study

Hemorrhage Control for Major Traumatic Vascular Injuries

Phase II: A Prospective Observational Study of Non-Compressible Torso Hemorrhage (NCTH)

Proposal Number: 13057176

Sponsor: United States Department of Defense

Principal Investigator:
John Holcomb, M.D.
Vice Chair and Professor of Surgery
Director, Center for Translational Injury Research
Jack H. Mayfield, M.D. Chair in Surgery
University of Texas Health Science Center
6410 Fannin, Suite 1100 Houston, TX 77030
Phone: 713-500-5493
Fax: 713-500-0683
John.Holcomb@uth.tmc.edu

Roles and Responsibilities:
Study Principal Investigator will be responsible for all aspects of the study.

Co-Investigators will assist the Study Principal Investigator in data collection, management, analysis, and interpretation.

Site Principal Investigators will be responsible for all aspects of the study conducted at their institution and will be responsible for reporting all study related activities, data and unanticipated events to the Study Principal Investigator.

Research Nurses/Coordinators will be responsible for coordinating the study at each institution including IRB approvals and communications; data completion and submission to UT Houston.

Research Assistants/Associates will assist the Research Nurse/Coordinator in collecting the data for the study.

Data Manager will oversee the data sent to UT Houston, data entry into the database and ensure appropriate storage of all data is maintained.

Site Locations:
1. University of Texas Health Science Center Houston (UTHealth)
   PI: John Holcomb, M.D.

2. Baylor College of Medicine (BCM)
   PI: Ramyar Gilani, M.D.

3. University of Texas Health Science Center at San Antonio (UTHSCSA)
   PI: Brian Eastridge, M.D.

4. US Army Institute of Surgical Research (USAISR)
   Co-PIs: Kevin Chung, M.D. and Valerie Sams, M.D.

Table of Contents

Study Title: Hemorrhage Control for Major Traumatic Vascular Injuries, Phase 2: A Prospective, Observational Study of Non-Compressible Torso Hemorrhage (NCTH).

Background

Patients presenting with hemodynamic instability associated with non-compressible torso vascular injury and hemorrhage are challenging to treat. Mortality rates of injured patients presenting with hemodynamic instability exceed 50% in several military and civilian studies and hemorrhage is the leading cause of death in the ongoing war.[1-4] Non-compressible torso hemorrhage (NCTH) has recently been defined as hemorrhage arising from trauma to vessels of the torso, pulmonary parenchyma, solid abdominal organs and disruption of the bony pelvis resulting in hypotension or shock, and has been identified as the remaining focus area for improved hemorrhage control interventions.[5] These injuries are particularly important and difficult to treat on today's battlefield, where tourniquets and hemostatic dressings are widespread and effective for compressible extremity issues, but not for NCTH.

Research is required to develop rapidly deployable, less invasive endovascular methods to monitor hemodynamics, control hemorrhage, sustain central myocardial and cerebral perfusion and stabilize vascular disruption within the torso as well as reduce mortality from NCTH. Specific methods should be developed to manage vascular disruption and hemorrhage from the junctional regions between the torso and the extremities. One potential way to reduce mortality from NCTH is the use of advanced systems approaches like hybrid operating rooms (ORs). Use of endovascular balloon occlusion within or outside a Hybrid OR may also reduce mortality. Recent efforts in the development of these techniques and methods have mainly focused on combat casualties, but previous studies have found that many similarly injured and bleeding trauma patients are admitted to civilian trauma centers, albeit with fewer severe extremity hemorrhage injuries than in the combat arena. However, there are few data regarding NCTH, so the first course of action should be to better characterize the problem first.

<u>Non-Compressible Torso Hemorrhage (NCTH)</u>

Severe trauma to or disruption of the following vascular structures leads to NCTH, shock and death: 1) named large (i.e. axial) vessels; 2) vessels proximal to or within the parenchyma of the kidney, liver, and spleen; 3) vessels within the parenchyma of the lung; or 4) vessels of the pelvis. Identifying patients with these injuries quickly is paramount. However no studies have identified the precise anatomic location or number of bleeding vessels among NCTH patients and specific vessels are frequently not named in the medical record. If new interventions and devices are to be evidence-based and intelligently designed, it is of utmost importance to obtain these types of data, which this proposal will deliver.

We have reviewed trauma registry data for 63 patients with a systolic blood pressure (SBP) < 100 who underwent a laparotomy within 2 hours of admission at a single Level 1 trauma center. Mortality in these patients was 33% and they averaged 16 days in the hospital, reflecting that patients with NCTH are critical and methods to improve their outcomes must be found. These patients were treated in a center with practices similar to those found on the battlefield (1:1 resuscitation, use of tourniquets, pelvic stabilization, etc.). Table 1 shows the number of trauma laparotomies within the first 24 hours after admission and the number of

trauma laparotomies within 2 hours of admission with an SBP<100 for all four proposed sites in 2012. These numbers provide a good estimate of the number of patients who may be classified as having NCTH and/or may benefit from alternate hemorrhage-control techniques.

Table 1. Trauma exploratory laparotomies at the 4 proposed sites in 2012

	Number of trauma laparotomies in 1st 24 hrs	Number of trauma laparotomies within 2 hours of admission and SBP<100 mm Hg
University of Texas Health Science Center at Houston	234	63
Baylor College of Medicine	225	50
University of Texas Health Science Center at San Antonio	184	60
San Antonio Military Medical Center/ US Army Institute of Surgical Research	114	22

Treatment delays in NCTH patients

We recently conducted a 3-year registry-based study of a subset of NCTH patients, those with pelvic fracture and hemorrhage, comparing 146 night and weekend patients to 45 similarly injured patients arriving during normal business hours. These patients are a subset of NCTH patients. We presented this research at the Eastern Association for the Surgery of Trauma meeting in January 2013 and the manuscript is currently under review. Time to angiography was significantly increased among after-hours patients compared to regular-hours patients. Eleven percent of after-hours patients died awaiting Interventional Radiology (IR) compared to none of the patients admitted during regular hours. Among those surviving long enough to receive IR, after-hours patients had a 94% increase in mortality compared to patients admitted during regular hours. While this was a single center retrospective study, it suggests that the majority of patients with pelvic fracture and hemorrhage are admitted at night and on weekends and that these patients may be subject to a higher risk of mortality due to delays in treatment to control bleeding.

Treatment delays may be due in part to the physically separate locations of trauma ORs and IR suites/ORs in most civilian Level 1 trauma centers. These "locational silos" can result in poor patient outcomes because they require risky patient transports throughout the hospital and handoffs between multiple providing teams. For this reason, trauma hybrid ORs, surgical suites with advanced imaging equipment mounted to the ceiling or floor, are being planned in many centers. In trauma hybrid ORs, all equipment and technical support for treating trauma patients are centrally located and clinical specialists come to the patient instead of transporting the patient to the specialist. This patient-centric concept would decrease time to a hemorrhage control intervention and likely improve patient care and outcomes. In a trauma hybrid OR, it is also possible to transition from minimally invasive to open surgical procedures in emergent situations without the need to transport unstable trauma patients, reducing transfusion requirements, ventilator times, the risk of infection and total procedure times especially in many trauma centers in which interventional radiologists do not provide 24/7 in-hospital coverage.

New devices and monitoring in conjunction with a hybrid OR may facilitate the optimal delivery of care for patients with NCTH. However, published evidence on the clinical benefits of hybrid ORs is limited, especially for patients with traumatic injuries. For this reason, UTHealth has formed an interest group based on developing the hybrid OR concept for trauma. This Trauma Hybrid OR (THOR) and catheter-based hemorrhage control group met February 26-27, 2013. At this meeting, 60 physicians and nurses from across North America representing six specialties discussed the clinical problems, the technology needed to improve patient care, patient flow, treatments, credentialing and a skills lab for acute care surgeons. From this meeting we have generated an American Association for the Surgery of Trauma-approved multi-center study and will publish a summary report. This is a rapidly changing field and we are mindful that future changes may impact this project. Additionally the THOR interest group has galvanized us and others to more closely examine the immediate opportunities for improved catheter based hemorrhage control of patients suffering NCTH.

Treatment of patients with NCTH

Major improvements have been made in extremity injury hemorrhage control on the battlefield with tourniquets, hemostatic dressings and junctional hemorrhage control devices which have moved into civilian care and are employed in the four participating centers (University of Texas Health Science Center at Houston [UTHealth], Baylor College of Medicine [BCM], University of Texas Health Science Center at San Antonio [UTHSCSA], and US Army Institute of Surgical Research [USAISR]). However, other opportunities exist to improve care for NCTH patients through rapid endovascular control of vascular injury.[6] ED-based endovascular balloon occlusion of the aorta holds promise for patients with NCTH by mitigating hemorrhage and increasing central aortic pressure until definitive hemostasis can be achieved.[7, 8] Achieving aortic occlusion has traditionally required a thoracotomy or a laparotomy for aortic exposure in the ED with direct aortic compression performed to evaluate and treat reversible causes of cardiovascular collapse.[9-11] Where resuscitative thoracotomy is employed, the mortality rate, morbidity, and cost of the procedure is high due to the nature of the injuries.[12] High mortality rates (88%) are also found among combat casualties who undergo ED thoracotomy.[7] Similarly, aortic occlusion for extra-thoracic injuries via thoracotomy or laparotomy carries a high mortality rate and current management protocols are hampered by small sample sizes.[9,13] Notably, the four proposed clinical sites all are staffed by surgical leaders who actively utilize catheter-based interventions. We expect additional catheter-based interventions to be performed at all four sites over the next two years of this proposed study. This technique is in rapid evolution and will change over the duration of this proposed study. Through structured documentation of the bleeding vessels and hemorrhage control maneuvers, we can further this field with high quality data that will inform evidence-based device design and intervention. Acute care surgeons at UTHealth have utilized the catheter-based hemorrhage control technique in 12 patients to date and we expect more in the future. Placement in the emergency department is feasible and may not require advanced imagining equipment.

Another area with limited existing literature is the quantification of vascular morphometry of the human torso and junctional regions. Only one published study has addressed this issue in

relation to Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA).[14] In this study, the authors suggest that REBOA has not been applied broadly partly because of the skills needed to perform REBOA may not be well understood by non-vascular surgeons. Generally, placement of the balloon for resuscitation should be in Aortic Zones 1 or 3 (see Figure 1)[14] and current recommendations require placement under fluoroscopic guidance. However, this may not be possible outside of well-equipped Level 1 trauma centers. For this reason, easily obtained external measures of the torso are invaluable if they correlate well with vascular insertion lengths and therefore can be used in trauma settings without fluoroscopic capabilities. For this reason, this proposed site-specific study will obtain CT images in order to characterize population-based morphometry and predict insertion depth.

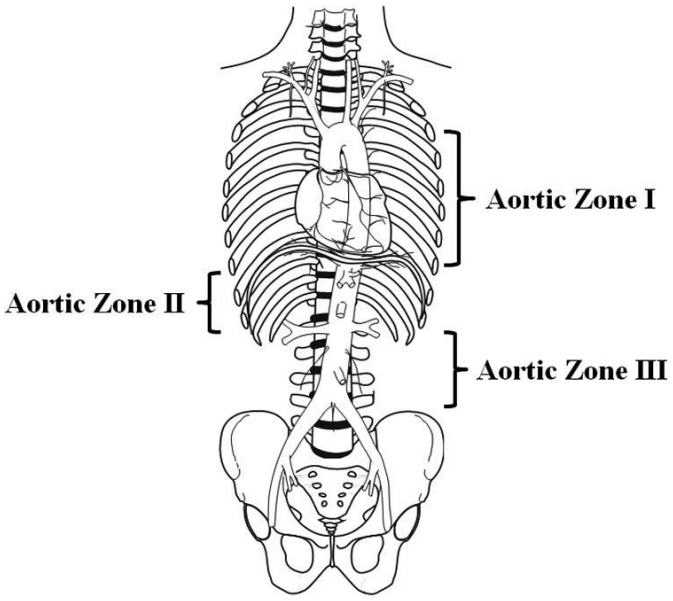


Figure 1. Aortic zones of interest in Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) copied from Stannard et al., 2011.[14] "Zone I extends from the origin of the left subclavian artery to the celiac artery and is a potential zone of occlusion. Zone II extends from the celiac artery to the lowest renal artery and is a no-occlusion zone. Zone III exists from the lowest renal artery to the aortic bifurcation. REBOA in this zone may provide particular utility for instances of pelvic and junctional femoral (contralateral) hemorrhage."[29]

Retrospective Study

A retrospective data study captured specific non-compressible torso hemorrhage data at centers who will be participating in this study. The data was from a five year time period (January 1, 2008 to December 31, 2012). Data captured include injury details, specific named vessels injured, diagnosis and management of the torso vessel hemorrhage, complications related to intervention, and discharge information (date/time, destination). The objective of this study was to identify the frequency of specific vessels injured, techniques utilized for diagnosis and management, and clinical outcomes related to non-compressible torso hemorrhage.

Delphi Meeting

The Delphi meeting was held on March 7, 2016. The attendees included the participating center's principal investigators and coordinators, military and civilian experts, and investigators and staff from the Houston Clinical and Data Coordinating Centers. Results from the retrospective study were reviewed followed by discussion on how to proceed with implementation of the prospective, observational study. Specific points discussed were primary and secondary objectives, eligibility criteria, and data elements to be collected.

Hypothesis
We hypothesize that endovascular control techniques improve survival and decrease exsanguination and complications compared to traditional open vascular surgical techniques in NCTH patients in four leading Level 1 trauma centers, after controlling for injury severity and site.

Objective
To determine current practice patterns for the treatment of patients with non-compressible torso hemorrhage among 4 clinical sites using a prospective observational study design. These data will inform future adoption and development of catheters, devices, and training required for surgeons implementing endovascular and catheter-based hemorrhage control.

The specific aims are as follows:

1. Identify and document the specific location, size and name of all vessels/organs requiring hemorrhage control among patients with NCTH.
2. Determine the frequency of methods for endovascular and open vascular repair and management used among NCTH patients.
3. Determine time to hemorrhage control and relative effectiveness of each hemorrhage control treatment with regards to all-cause mortality, exsanguination, and complications adjusting for injury severity.
4. Identify predictors of mortality (all-cause and cause-specific) and complications after NCTH.
5. Quantify the applicable vascular morphometry of the human torso using standard imaging software to measure diameter and length of the torso vessels and relative distances between major aortic branch vessels, external measure of torso extent, and Aortic Zones as defined by Stannard[14]
6. Define specific vascular injuries that may be amenable to existing or future endovascular repair and management techniques

Study Design
This is a prospective, observational study which will be conducted at four Level 1 trauma centers in the State of Texas.

Study Population
The target population for this prospective observational study will be all trauma patients who meet the eligibility criteria with known or suspected NCTH admitted to one of the four participating centers.

NCTH has been defined in the literature[27] as the presence of vascular disruption from any of the following categories: 1) Named axial torso vessel disruption, 2) Solid organ injury ≥ grade 4 (liver, kidney or spleen) with concomitant hemorrhagic shock or immediate operation, 3) Thoracic cavity injury (including lung), and 4) Pelvic fracture with ring disruption. The study procedures will identify these patients prospectively and start data collection before diagnostic testing has confirmed the diagnosis to get the most representative population of NCTH patients possible. As these conditions are often unknown at admission,

data collection will commence on a wider population of patients who potentially have these injuries in order to obtain a comprehensive and representative sample of patients with NCTH. See Subject Screening below for additional information.

Inclusion Criteria

1) 15 years of age or older or >/= 50 kg body weight if age unknown.
2) Has a truncal procedure (endovascular or open) within 4 hours of emergency department (ED) arrival
3) Admitted to one of four participating Level 1 trauma centers

Exclusion Criteria

1) Prisoners, defined as those who have been directly admitted from a correctional facility

Study Procedures

Subject Screening

Clinical research staff will be available on a 24/7 basis at the participating centers to screen and collect data on all highest activation trauma patients upon arrival to the ED and who meet study eligibility criteria. Direct observation will continue until 1) the patient completes the truncal procedure and arrives at a nursing unit, 2) the patient expires, or 3) no surgical or endovascular procedures have been initiated within the first 4 hours after ED arrival.

All patient care will use the participating center's standards, policies and procedures. No study interventions, drugs, or devices will be assigned to subjects as part of this observational study.

Informed Consent

A waiver of informed consent will be requested for this observational study for the following reasons:

1. The research involves no more than minimal risk – this is a prospective observational study not involving patient randomization to a treatment or intervention group.
2. The waiver will not adversely affect the rights and welfare of the patient – data regarding the standard of care procedures will be collected prospectively and there will be no contact between patient and research staff. Data collected for study purposes will be de-identified to prevent confidentiality breaches.
3. The research could not practically be carried out without waiver – this is a prospective, observational study involving no study intervention or contact with the subject.

Data Collection

Direct data collection will include:

- Prehospital information (obtained from the prehospital clinical staff): times, injury details, life-saving interventions (LSIs), fluid and blood product usage, and vital signs.
- In-patient information: vital signs, LSIs, fluid and blood product usage, routine laboratory results (including lactate, base, TEG, INR, PTT), diagnostic procedures, interventional procedures, hemorrhage control devices, procoagulant medications, and time to hemostasis.

Additional data to be collected during the subject's inpatient hospitalization or up to 30 days (whichever occurs first) will include interventional procedures, CT (CAT Scan) and IR (Interventional Radiology) images, complications, date and time of death or discharge to another destination (home, long term care facility, rehabilitation facility or skilled nursing facility), cause of death, injury severity scores and ventilator/intensive care unit (ICU)/ hospital free days. Complications will include rebleeding resulting in unplanned OR/IR, thromboembolic (myocardial infarction [MI], stroke, deep vein thrombosis [DVT], pulmonary embolism [PE], mesenteric thrombosis), sepsis, infections, and aortic occlusion (access artery thromboembolization, distal limb arterial thromboembolization). Definitions for these complications will be included in the manual of operations (MOO).

The cause of death for all study subjects will be classified into one or more of nine groups: Exsanguination/Hemorrhagic Shock, Traumatic Brain Injury, Respiratory/Pulmonary Contusion/Tension Pneumothorax, Sepsis, Multi-Organ Failure, Cardiovascular Event (MI, Stroke), Pulmonary Embolism, Other, or Unknown. The definitions for each group will be included in the MOO. The participating center's Principal Investigator (PI) will determine all causes of death and then determine the primary cause of death. The participating centers will provide a brief death summary to the study PI who will review and adjudicate the cause of death assessment.

Additional data will be collected from medical records including prehospital run sheets and the trauma registry database. Detailed instructions regarding the data collection will be included in the MOO. The data will be entered on a standardized case report forms (CRFs) and transferred to a secure web-based electronic database. Each subject will be assigned a study specific number; no identifying data will be entered in the electronic database. Each research staff member entering data into the database will be given a specific user ID and password to ensure security is maintained and reduce any risk of breach of patient confidentiality.

At the Houston site only, imaging of the vascular injuries will be obtained to measure diameter and length of the torso vessels and relative distances between major aortic branch vessels, external measure of torso extent, and Aortic Zones as defined by Stannard.[14]

Sample Size
We will enroll all eligible patients identified with NCTH during the 12-months of enrollment. We expect between 600 and 1200 patients to be enrolled at the 4 participating sites. As of 2012, nearly 50% of patients at our institution received endovascular versus open repair procedures. Therefore we prospectively expect a 50-50% split in procedure types, which maximizes power to detect significant differences in outcomes. The power to detect an 8% improvement in mortality at 3 hours using a 2-sided alpha of 0.05 and open procedure mortality rate of 0.20 is 76.33% for 600 patients and 96.64% for 1200 patients. Our previous study showed 75/369 = 0.203 deaths for initial open procedures.

Analyses described below will also be subset by injury type: thoracic and vascular injuries, and location: chest, abdomen, and pelvis. The power to detect MCID will be slightly lower for these secondary analyses.

Data Storage and Management
Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information. All data collected for the purposes of this study will be maintained in accordance with HIPAA rules and regulations. The patients will be identified by a specific, assigned study number which is not affiliated with the hospital medical record number.

The subjects will be identified by a study number only. All hard copy source documentation will be kept in a secured, locked cabinet in the site‘s research coordinator‘s office. Only study coordinators at each site will have access to master patient logs that link individual patient identifiers with study ID numbers. All study documents will be maintained in a secure location for the time frame designated by each participating site‘s requirements. The electronic data will be entered and maintained on a password protected web-based program designed for this trial.

Data entry will occur on paper clinical report forms (CRFs) and entered into REDCap. The REDCap database was designed to support data entry, validation, and export for research studies. The database works over the web and access can be granted to users based on level of access required. Data entry can occur on any device, including a phone, tablet, laptop, and desktop computers with or without internet access. The system supports all modern security protections to prevent unauthorized access. In addition, a full history is maintained to ensure data accuracy and allow for scheduled and randomized auditing. Data validation can occur on a per field or per patient basis to prevent against spurious data entry. Data exports can be set to occur automatically to appropriate staff over email or from the web frontend to ensure data quality or for analysis.

All clinical sites will enter their data into REDCap and keep a copy of the paper CRF at the site. The REDCap database is housed at UTHealth in a cluster is composed of multiple servers, which provide redundant access to the data in the event of a hardware failure to one

of the servers. This cluster is maintained behind a firewall, which is not accessible from the internet without a secure network connection. The data is backed up nightly.

Error Checking. Parameters that are not measured (e.g., routine laboratory tests not possible or not ordered by the attending physician due to the patient's critical condition, etc.) will be distinguished from missing values by a unique code and documented during data collection. Each item on the data entry forms will have validity checks performed to ensure that the data entered are accurate and that items are not skipped during entry by mistake. Range checks developed by both clinical and statistical investigators will be programmed into the study's data entry software to avoid missing values as much as possible and prevent out-of-range values at the point of data entry. When the data record is saved, a form status field will be updated to indicate the current status of the form. There are four status states that the form can have. These statuses are: the form is incomplete, the form is complete, the form was saved with errors, and the form is complete with errors.

Data will be monitored by the Data Manager for completeness and accuracy. Missing values and extreme outliers (e.g., > 5 standard deviations from mean) will be brought to the immediate attention of the study coordinator and resolved as quickly as possible. DCC staff will have access to listings of subject specific errors needing correction by site. The sites will be queried weekly for error correction and the corrections will be entered at the DCC. All site investigators and staff will be trained to follow regulatory procedures when making any changes in the paper forms or source documentation (no erasures, cross through error, write in correction, date, and initial). Once a record has been saved by the DCC as complete, changes to the record will not be allowed. At the end of the study after all possible corrections are made, the database will be locked and further changes will not be made.

Investigator Resources and Reporting. A secure web-based portal will be provided through which management personnel, study investigators and coordinators can log in to review status and other reports about the studies that they are permitted to access, for example recruitment reports and reports on data quality. Quarterly reports to the funding agency and manuscripts in progress may also be available on this secure site.

Archiving the Final Dataset for Public Use. Once the database is locked for analyses and primary study publications are completed and submitted, the DCC will follow DoD guidelines related to archiving de-identified data and making it publically available.

Quality Assurance Training. Training of research staff and nurses who will be responsible for data collection is planned for this study. A manual of operations (MOO) developed by the DCC team will provide standard definitions of all study variables (i.e., data elements) and describe all data collection and data entry procedures in detail. Copies of the MOO will be distributed to all participating sites to be used in training each site's research team and will be available on the study website through the DCC section of the study website. In addition to the planned training calls and webinars, each site will be responsible for the complete education of their personnel in the conduct of this proposed study.

Statistical Analysis Plan

Data will be cleaned, edited and prepared for comprehensive summary descriptive analyses. Descriptive analyses (tabulations and measures of central tendency) including graphical displays (e.g., histograms) will be used for initial characterization and summarization of the data. The descriptive analyses will also help detect any remaining missing values, outliers and unexpected patterns across covariates, both within and across sites. The descriptive analyses will also help to spot possible trends of interest or importance. All data cleaning/statistical analyses will be performed using SAS v.9.4, STATA 14, and R. All below analyses will also be subset by injury type: thoracic and vascular, and location: chest, abdomen, and pelvis.

Aim 1: Descriptive statistics (means, medians, interquartile range, and proportions) will be performed to achieve Aim 1. For example, frequency of vessels requiring hemorrhage control will be assessed by a proportion with a 95% confidence interval. All other variables describing the vascular injuries will be handled similarly. All results will be stratified by site, and variation by site reported.

Aim 2: Descriptive statistics (means, medians, interquartile range, and proportions) will be performed to achieve Aim 2, determining current practice. For example, frequency of intra-arterial balloon occlusion device placement will be assessed by calculating the number of uses of the method divided by the number of times it could have been used appropriately. The denominator of this proportion will be determined by a standardized assessment by site PIs. All other variables describing patient care practice will be handled similarly. All results will be stratified by site, and variation by site reported.

Aim 3: Descriptive statistics (means, medians, interquartile range, and proportions) will be performed to examine time to hemorrhage control. Time to hemorrhage control will be computed as the time period from the time of injury or ED arrival to the time of definitive anatomic hemostasis. Patients who die, are declared DNR, or have care withdrawn before definitive anatomic hemostasis has been declared will be classified as "died before hemostatic control was achieved." Chi square tests will be used to compare the study groups on whether hemorrhage control was ever achieved (yes/no), and Cox proportional hazards modeling adjusting for site (via shared frailty models) will be used to compare groups on time to hemorrhage control, adjusting for other covariates (e.g., age, sex, prehospital vital signs, mechanism of injury severity, etc.).

Effectiveness of each hemorrhage control treatment identified in Aim 2 will be determined by calculating the proportion of patients who achieved hemostatic control by a specific hemorrhage control treatment among all patients who received that hemorrhage control treatment. Logistic regression modeling will be used to compare groups on effectiveness of each specific hemorrhage control treatment, adjusting for other covariates. Stratification by site will examine the potential for site variation in clinical practice.

Aim 4: We will use multivariable logistic regression to identify predictors of mortality and complications after major vascular and solid organ injuries in the torso, adjusting for the potential confounding or modifying effects of important covariates and including site as a

random effects variable to adjust for any unmeasured site heterogeneity in resuscitation practices. We will use purposeful model building and variable selection strategies to choose among candidate covariates, including stepwise logistics regression model selection and lasso variable selection. To increase the ability of our analysis to detect a significant associations between covariates and outcomes, we will use Cox regression modeling to model time-to- hemostatic control, death and/or complications as a function of procedure type and covariates. As in Aim 3, the Cox regression will account for unmeasured site differences in resuscitation practices via use of a shared frailty (accommodating correlation within site). We will also explore time-dependent Cox modeling to reduce the potential for survival bias.

Because we expect the two hemorrhage control groups to be very different on underlying covariates and risk factors such as injury type and location, we will pursue propensity scoring as an exploratory analysis. The purpose of propensity scoring is to establish a covariate or risk factor "distance" on which to match patients receiving 2 different procedures, allowing us to obtain a causal effect of procedure on outcome resembling that which would be obtained from a randomized controlled trial. This metric will be constructed using a logistic regression where all covariates will be used to predict procedure type. After matching patients using state-of-the-art methodologies with which our group has substantial expertise, we will assess the effect of treatment on outcomes in the propensity-matched data set using a conditional logistic regression (for binary outcomes) or Cox proportional hazards model (for time-to-event outcomes). Propensity score analyses based on stratification of the propensity score into quintiles will also be explored. The latter method can be more powerful than matching because it uses all of the data, however it may give less precise estimates if there is a high level of disparateness between the two procedure groups.

All analyses described above will use initial procedure type in an intent-to-treat type analysis. A secondary analysis will be performed using definitive (final) procedure type.

Aim 5: Descriptive statistics (means, medians, proportions) will be performed to quantify the vascular morphometry of NCTH patients.

Aim 6: Descriptive statistics (means, medians, proportions) will be performed to identify specific vascular injuries amendable to existing or future endovascular repair and management techniques using information derived from the survey questions to the attending surgeon.

Risk and Injury
This is a minimal risk study. The only potential risk to the subjects is the potential for breach of confidentiality. All measures will be taken to ensure that the subject's information is maintained in a locked, secure office or on a password protected computer database.

Benefits
Potential benefits will include improved treatment management guidelines for future trauma patients experiencing non-compressible torso hemorrhage.

Compensation
No compensation will be involved in this prospective, observation study.

Confidentiality
All measures will be taken to ensure subject confidentiality is maintained throughout the study.

Adverse Events
All unanticipated problems involving risk to subjects or others related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012

Changes to Protocol
Major modifications to the research protocol and any modifications that could potentially increase risk to the subjects must be submitted to each center's local Institutional Review Board as well as the USAMRMC HRPO for approval prior to implementation. Major modifications include a change in Principal Investigator, change or addition of an institution, changes to the consent process, change or addition to the study population or any change which could potentially increase the risk to the subjects.

References Cited

1. Costantini TW, Bosarge PL, Fortlage D, Bansal V, Coimbra R. Arterial embolization for pelvic fractures after blunt trauma: are we all talk? *American journal of surgery* 2010;200:752-757; discussion 757-758.
2. Eastridge BJ, Hardin M, Cantrell J, Oetjen-Gerdes L, Zubko T, Mallak C, Wade CE, Simmons J, Mace J, Mabry R, et al. Died of wounds on the battlefield: causation and implications for improving combat casualty care. *The Journal of trauma* 2011;71:S4-8.
3. Holcomb JB, McMullin NR, Pearse L, Caruso J, Wade CE, Oetjen-Gerdes L, Champion HR, Lawnick M, Farr W, Rodriguez S, et al. Causes of death in U.S. Special Operations Forces in the global war on terrorism: 2001-2004. *Annals of surgery* 2007;245:986-991.
4. Kelly JF, Ritenour AE, McLaughlin DF, Bagg KA, Apodaca AN, Mallak CT, Pearse L, Lawnick MM, Champion HR, Wade CE, et al. Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 versus 2006. *The Journal of trauma* 2008;64:S21-26; discussion S26-27.
5. Stannard A, Morrison JJ, Scott DJ, Ivatury RA, Ross JD, Rasmussen TE. The epidemiology of noncompressible torso hemorrhage in the wars in Iraq and Afghanistan. *The journal of trauma and acute care surgery* 2013;74:830-834.
6. Rasmussen TE, Dubose JJ, Asensio JA, Feliciano DV, Fox CJ, Nunez TC, Sise MJ. Tourniquets, vascular shunts, and endovascular technologies: esoteric or essential? A report from the 2011 AAST Military Liaison Panel. *The journal of trauma and acute care surgery* 2012;73:282-285.
7. Edens JW, Beekley AC, Chung KK, Cox ED, Eastridge BJ, Holcomb JB, Blackbourne LH. Longterm outcomes after combat casualty emergency department thoracotomy. *Journal of the American College of Surgeons* 2009;209:188-197.
8. Mattox KL, Feliciano DV. Role of external cardiac compression in truncal trauma. *The Journal of trauma* 1982;22:934-936.
9. Burlew CC, Moore EE, Moore FA, Coimbra R, McIntyre RC, Jr., Davis JW, Sperry J, Biffl WL. Western Trauma Association critical decisions in trauma: resuscitative thoracotomy. *The journal of trauma and acute care surgery* 2012;73:1359-1363; discussion 1363-1354.
10. Seamon MJ, Fisher CA, Gaughan JP, Kulp H, Dempsey DT, Goldberg AJ. Emergency department thoracotomy: survival of the least expected. *World journal of surgery* 2008;32:604-612.
11. Seamon MJ, Pathak AS, Bradley KM, Fisher CA, Gaughan JA, Kulp H, Pieri PG, Santora TA, Goldberg AJ. Emergency department thoracotomy: still useful after abdominal exsanguination? *The Journal of trauma* 2008;64:1-7; discussion 7-8.
12. Passos EM, Engels PT, Doyle JD, Beckett A, Nascimento B, Jr., Rizoli SB, Tien HC. Societal costs of inappropriate emergency department thoracotomy. *Journal of the American College of Surgeons* 2012;214:18-25.
13. Practice management guidelines for emergency department thoracotomy. Working Group, Ad Hoc Subcommittee on Outcomes, American College of Surgeons-Committee on Trauma. *Journal of the American College of Surgeons* 2001;193:303-309.

14. Stannard A, Eliason JL, Rasmussen TE. Resuscitative endovascular balloon occlusion of the aorta (REBOA) as an adjunct for hemorrhagic shock. *The Journal of trauma* 2011;71:1869-1872.
15. Holcomb JB, Wade CE, Brasel KJ, Vercruysse G, MacLeod J, Dutton RP, Hess JR, Duchesne JC, McSwain NE, Muskat P, et al. Defining present blood component transfusion practices in trauma patients: papers from the Trauma Outcomes Group. *The Journal of trauma* 2011;71:S315-317.
16. Holcomb JB, Del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, Alarcon LH, Bai Y, Brasel KJ, Bulger EM, et al. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study: Comparative Effectiveness of a Time-Varying Treatment With Competing Risks. *Arch Surg* 2012:1-10.
17. Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM, Altman DG, Blazeby JM, Boutron IC, Campbell WB, Clavien PA, et al. Evaluation and stages of surgical innovations. *Lancet* 2009;374:1089-1096.
18. Ergina PL, Cook JA, Blazeby JM, Boutron I, Clavien PA, Reeves BC, Seiler CM, Altman DG, Aronson JK, Barkun JS, et al. Challenges in evaluating surgical innovation. *Lancet* 2009;374:1097-1104.
19. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, Nicholl J, Aronson JK, Barkun JS, Blazeby JM, et al. No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009;374:1105-1112.
20. U.S. Census Bureau. Annual Estimates of the Resident Population for Incorporated Places over 50,000, ranked by July 1, 2011 Population. Accessed April 25, 2013. Available.
21. Davis JA, Gilani R, Al-Najjar R, Tsai PI, Wall Jr MJ. Operative challenges in management of concurrent interrupted aortic arch and descending thoracic aortic aneurysm. *Journal of vascular surgery* 2013.
22. Gilani R, Saucedo-Crespo H, Scott BG, Tsai PI, Wall MJ, Jr., Mattox KL. Endovascular therapy for overcoming challenges presented with blunt abdominal aortic injury. *Vascular and endovascular surgery* 2012;46:329-331.
23. Gilani R, Tsai PI, Wall MJ, Jr., Mattox KL. Overcoming challenges of endovascular treatment of complex subclavian and axillary artery injuries in hypotensive patients. *The journal of trauma and acute care surgery* 2012;73:771-773.
24. Wall MJ, Jr., Tsai PI, Gilani R, Mattox KL. Open and endovascular approaches to aortic trauma. *Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital* 2010;37:675-677.
25. Dalkey NC, O H. An experimental application of the Delphi method to the use of experts. *Management Science* 1963;9:458-467.
26. Linstone HA, M T, eds. *The Delphi Method: Techniques and Applications*. Addison-Wesley Publishing Co.; 1975.
27. Morrison JJ, Rasmussen TE. Noncompressible torso hemorrhage: a review with contemporary definitions and management strategies. *The Surgical clinics of North America* 2012;92:843-858, vii.
28. Nunez TC, Voskresensky IV, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? *The Journal of trauma* 2009;66:346-352.

29. Martinelli T, Thony F, Declety P, Sengel C, Broux C, Tonetti J, Payen JF, Ferretti G. Intra-aortic balloon occlusion to salvage patients with life-threatening hemorrhagic shocks from pelvic fractures. *The Journal of Trauma* 2010;68:942-948.

9/20/16

Case Report Forms

Document Version Date: 05.24.16

Table of Contents

General Instructions:

- Enter all dates in MM/DD/YY format. Enter all times in HH:MM using 24hr clock format.
- Print additional form pages if needed. Label additional form pages using a decimal point followed by sequential numbers. (Example: Page 5.01, 5.02)
- Use the following codes in data fields with unknown values:

NA = Not Applicable (e-CRF Code –995)	ND = Not Detectable (e-CRF Code –996)	NK = Unknown (e-CRF Code –997)
NP = Not Palpable (e-CRF Code –998)	NR = Not Recorded/Not Done (e-CRF Code –999)	

Study ID # ___ ___ ___ ___ ___ ___

___

CRF Version Date 2016 MAY 24

Form 1: Verification of Eligibility/Screening

1. ED Arrival: Date: __ __/__ __/__ __ Time: __ __:__ __ ***(TIME ZERO)***
(mm/dd/yy) *(24hr Clock in hh:mm)*

Inclusion Criteria: *(To be eligible, all questions must be answered "**YES**")*

1. Age (Est. ≥ 15 yr. or ≥ 50 kg if age unknown) ☐ Yes ☐ No
2. Evidence of truncal injury requiring OR and/or IR for truncal procedure within 4 hours of ED arrival ☐ Yes ☐ No

Exclusion Criteria: *(To be eligible, all questions must be answered **"NO"**)*

1. Prisoners, defined as those who have been directly admitted from a correctional facility ☐ Yes ☐ No

Form 2: EMS / Pre-Hospital Care

1. Estimated Injury date/time known: ☐ Yes↓ ☐ No

   Date: __ __/__ __/__ __ Time: __ __:__ __
   (mm/dd/yy) *(24hr Clock in hh:mm)*

2. EMS team call date/time known: ☐ Yes↓ ☐ No

   Date: __ __/__ __/__ __ Time: __ __:__ __
   (mm/dd/yy) *(24hr Clock in hh:mm)*

3. EMS team dispatch date/time known: ☐ Yes↓ ☐ No

   Date: __ __/__ __/__ __ Time: __ __:__ __
   (mm/dd/yy) *(24hr Clock in hh:mm)*

4. Was patient transported directly from the scene? ☐ Yes ☐ No

5. Was patient transferred from another facility? ☐ Yes ☐ No

FOR PATIENTS TRANSFERRED FROM ANOTHER FACILITY:

5.a. Date & Time of arrival to initial facility known: ☐ Yes↓ ☐ No

Date: __ __/__ __/__ __ Time: __ __:__ __
(mm/dd/yy) *(24hr Clock in hh:mm)*

5.b. Date & Time of departure from initial facility known: ☐ Yes↓ ☐ No

Date: __ __/__ __/__ __ Time: __ __:__ __
(mm/dd/yy) *(24hr Clock in hh:mm)*

5.c. Type of facility: ☐ Hospital ER ☐ Freestanding ER/clinic

6. Mode of transport to hospital (from scene or transferring facility)
   ☐ Ground ambulance ☐ Air ambulance ☐ Private vehicle

7. First available vital signs & GCS obtained by EMS transporting patient to receiving hospital:

Blood Pressure *(mmHg)*		Pulse *(beats/min)*	Respiratory Rate (breaths/min)
Systolic	Diastolic		
___ ___ ___	___ ___ ___	___ ___ ___	___ ___
	Palpable	Palpable	
	Yes / No	Yes / No	

GCS	
Record Component Scores **/** GCS Total Score	
E: ___ V: ___ M: ___	GCS Total Score:___
☐ Not Recorded	

8. Mechanism of Injury:

a. ☐ **Blunt Injury** *(Select all that apply)*

□ Fall □ MVC – Motorcycle □ MVC
□ Industrial Accident □ MVC – Bicycle □ Struck by/against (assault)
□ MVC – Pedestrian □ Bicycle
□ Motorcycle □ Other, *(Describe)*:_____

b. ☐ **Penetrating Injury** *(Select all that apply)*

□ Gunshot Wound □ Shotgun Wound □ Impalement
□ Stabbing (knife) □ Other, (*Describe*): _____

9. Did the subject receive any pre-hospital lifesaving interventions?

☐ Yes↓ (*Select all that apply*) ☐ No

□ Cardioversion □ Chest/Needle Decompression □ CPR
□ Intubation □ Trach/Cricothyrotomy □ Tourniquet
□ Pelvic Binder/Sheet □ Hemostatic Dressing □ TXA
□ X Stat □ Blood Products □ Junctional Tourniquet
□ Other, (*Describe*): _____

**For Pre-hospital blood products and IV fluids – enter information on Form 4
***For Pre-hospital procoagulants administered – enter information on Form 5

Form 3: Initial Hospital Information:

1. First available vital signs & GCS obtained upon arrival to ED:

Blood Pressure *(mmHg)*		Pulse *(beats/min)*	Respiratory Rate (breaths/min)
Systolic	Diastolic		
___ ___ ___	___ ___ ___	___ ___ ___	___ ___
	Palpable	Palpable	
	Yes / No	Yes / No	

GCS		Height	Weight
Record Component Scores **/** GCS Total Score		(cm)	(kg)
E: ___ V: ___ M: ___	___ ___ ___	___ ___ ___	___ ___ ___
☐ Not Recorded			

2. Admission FAST done? ☐ Yes↓ ☐ No

   Results: ☐ Positive↓ ☐ Negative ☐ Indeterminate

   If positive, select area: ☐ Abdominal ☐ Cardiac ☐ Both

3. Admission Labs (as obtained per Standard of Care guidelines)

   Hemoglobin (g/dL): _____
   Platelet count: _____
   pH: _____
   Lactate (mmol/L): _____
   Base: _____
   INR: _____
   PTT: _____

   Admission TEG done? ☐ Yes↓ ☐ No

   Type (check one): ☐ Rapid ☐ Kaolin
   R Time (Kaolin) / ACT (Rapid): _____
   K-Time: _____ Alpha Angle: _____ MA: _____ Ly30: _____

4. CPR in progress on ED arrival? ☐ Yes ☐ No

. 5. Did the subject receive any of the following lifesaving interventions in ED?

   ☐ Yes↓ (*Select all that apply*) ☐ No

   □ Aortic Clamping □ CPR □ ED Thoracotomy □ Pelvic Binder □ REBOA

CRF Version Date 2016 MAY 24

Form 4: IV Fluids & Blood Products Transfusion Record

*(Record blood products in **units** and all other fluids in **mLs** using the **codes** below for the 1st 24 hours only. Print additional pages if needed.)*

Location (LOCAT) Codes	
1	Prehospital
2	Emergency Room
3	Operating Room
4	Interventional Radiology
5	ICU
6	Intermediate Level Care
7	Nursing Unit
8	Other: *(Specify)*

Blood Products Codes			
1	Red Blood Cells (RBC)	6	Platelets – (Plt)
2	Plasma – Fresh Frozen (FFP)	7	Cryoprecipitate - (Cryo)
3	Plasma – Liquid (LP)	8	Autologous Blood (Auto)
4	Plasma - Thawed (TP)	9	Cell Saver - (Cell)
5	Plasma – FP24 (FP24)	10	Other Blood Product (OBL)

Colloids Codes		Crystalloids Codes	
1	Albumin (Alb)	7	Hypertonic Solution (Ht)
2	Hextend (Hex)	8	Lactated Ringers (LR)
3	Hespan (Hes)	9	Manitol (MN)
4	THAM Solution (THAM)	10	Normal Saline (NS)
5	Voluven (Vol)	11	Normosol (Norm)
6	Other Colloid (OCL)	12	Plasma-Lyte (PL)
		13	Other crystalloid (OCY)

MR: Data Collected from Medical Record Review	DO: Direct Observation

Complete for All Blood Products & IV Fluids							
LOCAT Code	Blood / Fluid Code	Start Date *(mm/dd/yy)*	Start Time *(24hr Clock in hh:mm)*	Amount/Units			
		/ /	:				
		/ /	:				
		/ /	:				
		/ /	:				
		/ /	:				
		/ /	:				

Form 5: Procoagulants *(1st 24 hours only.)*

Check here ☐ if no Procoagulant medications were given.

LOCATION CODE (LOCAT)	
1	Prehospital
2	Emergency Department
3	Operating Room
4	Interventional Radiology
5	ICU
6	Intermediate Level Care
7	Nursing Unit
8	Other *(Specify)*

Document Administration of the Following Medications Using the Codes Below	
1	Aminocaproic Acid *(Amicar) (g/hr.)*
2	Tranexamic Acid *(Cyclokapron) (mg/kg/hr.)*
3	Fibrinogen Concentrate *(Riastap) (mg/kg/hr.)*
4	Octaplex / Ocplex *(in ml.s)*
5	Prothrombin Complex Concentrate *(PCC)*
6	Recombinant Factor VIIa *(rFVIIa) (mics/kg)*
7	Factor VIII
8	Vitamin K
9	OTHER Procoagulant *(Specify with unit of measure)*

LOCAT	Administration Start Date *(mm/dd/yy)*	Administration Start Time *(24hr clock in hh:mm)*	Medication Code *(If other, Specify)*
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	
	/ /	:	

Form 6: Vascular Injury Information

Specific vascular structure(s) injured (**check ALL vascular structures injured):**

Arteries:
Heart
___ **Ascending aorta**
___ **Aortic arch**
___ ..Innominate (brachiocephalic) artery
___ ..Common carotid (intra-thoracic) artery (___ Rt ___ Lt)
___ ..Subclavian artery (___ Rt ___ Lt)
___ ….Internal thoracic artery (___ Rt ___ Lt)
___ ……Superior epigastric artery (___ Rt ___ Lt)
___ **Descending thoracic aorta**
___ ..Intercostal artery (___ Rt ___ Lt)
___ ..Superior phrenic artery (___ Rt ___ Lt)
___ **Abdominal aorta**
___ ..Inferior phrenic artery (___ Rt ___ Lt)
___ ..Celiac artery
___ ….Gastric artery (___ Rt ___ Lt)
___ ….Splenic artery
___ ….Hepatic artery (___ Common ___ Rt ___ Lt)
___ ..Superior mesenteric artery
___ **Supra-renal abdominal aorta**
___ **Juxta-renal abdominal aorta**
___ ..Renal artery (___ Rt ___ Lt)
___ **Infra-renal aorta**
___ ..Gonadal artery (___ Rt ___ Lt)
___ ..Lumbar artery (___ Rt ___ Lt)
___ ..Inferior mesenteric artery
___ ..Common iliac artery (___ Rt ___ Lt)
___ ….External iliac artery (___ Rt ___ Lt)
___ ……Inferior epigastric artery (___ Rt ___ Lt)
___ ….Internal iliac artery (___ Rt ___ Lt)

Pulmonary Circulation
___ Pulmonary artery (___ Rt ___ Lt)

Solid Organ Injury:
___ Lung (Grade _____)
___ Liver (Grade _____)
___ Spleen (Grade _____)
___ Kidney (Grade _____)

Veins:
___ ….Internal jugular (intra-thoracic) vein (___ Rt ___ Lt)
___ ….External jugular (intra-thoracic) vein (___ Rt ___ Lt)
___ ..Subclavian vein (___ Rt ___ Lt)
___ ..Innominate (brachiocephalic) vein (___ Rt ___ Lt)
___ ..Azygous vein
___ **Superior vena cava (SVC)**
Heart
___ **Inferior vena cava (IVC)**
___ ..Inferior phrenic vein (___ Rt ___ Lt)
___ **Retro-hepatic IVC**
___ ..Hepatic vein (___ Rt ___ Middle ___ Lt)
___ **Supra-renal/sub-hepatic IVC**
___ ..Suprarenal vein (___ Rt ___ Lt)
___ **Juxta-renal IVC**
___ ..Renal vein (___ Rt ___ Lt)
___ **Infra-renal IVC**
___ ..Gonadal vein (___ Rt ___ Lt)
___ ..Lumbar vein (___Rt ___ Lt)
___ ..Common iliac vein (___ Rt ___ Lt)
___ ….External iliac vein (___ Rt ___ Lt)
___ ….Internal iliac vein (___ Rt ___ Lt)

Portal circulation
___ Portal vein
___ ..Superior mesenteric vein
___ ..Inferior mesenteric vein
___ ..Splenic vein

Pulmonary circulation
___ Right pulmonary vein (___ Superior ___ Inferior)
___ Left pulmonary vein (___ Superior ___ Inferior)

Other: _____

_____

_____

_____

1. Of all venous injures, what was the primary venous vessel injured? _____

2. Of all arterial injuries, what was the primary arterial vessel injured? _____

3. Overall, what is the main source of bleeding requiring vascular repair? _____

A. Diagnosis of Major Vascular Injury

1. Modality utilized to make DEFINITIVE diagnosis of major vascular injury:
   - ☐ Operative exploration
   - ☐ Contrast-enhanced computed tomography / angiography (CTA)
   - ☐ Duplex ultrasound
   - ☐ Conventional contrast angiography in interventional radiology
   - ☐ Conventional contrast angiography in operating room (including hybrid OR/IR)

2. Injury Type as defined by diagnostic modality utilized:
   - ☐ Transection
   - ☐ Occlusion
   - ☐ Partial transection or flow limiting defect (e.g. dissection or intimal flap)
   - ☐ Pseudoaneurysm
   - ☐ Other: _____

B. Management of Major Vascular Injury

1. How was the major vascular injury managed **initially?** ☐ Open ☐ Endovascular

a. Date & time of initial procedure start: __ __/__ __/__ __ (*mm/dd/yy*) __ ___: ___ ___ (*24hr Clock in hh:mm*)

b. Location of initial procedure at start: ☐ ED ☐ IR suite ☐ OR ☐ Hybrid OR

c. Type of surgeon at initial management? ☐ Trauma ☐ Vascular ☐ Thoracic ☐ IR

If initial management was open:

1. Use of **damage control** techniques? ☐ Yes ↓ ☐ No (*If no go to Q2*)
   - ☐ Ligation of vascular injury?
   - ☐ Use of temporary vascular shunt?
     If yes, Type: _____ (Argyl, Javid, Sundt, other)
     Estimated dwell time of shunt: _____
   - ☐ Hepatic Packing
   - ☐ Pelvic Packing

2. Systemic anticoagulation utilized during initial open operation for major bleeding?
   ☐ Yes ↓ ☐ No
   If yes, list name: _____

3. Did definitive repair occur during the initial open procedure? ☐ Yes ☐ No
4. Was aortic occlusion performed during the initial open operation? ☐ Yes ☐ No

If yes, answer AO section questions

If initial management was endovascular:

1. Technique utilized to achieve vascular access:
   - ☐ Ultra-sound guided
   - ☐ Fluoroscopic guided, specify: ☐ C-arm or ☐ Fixed system
   - ☐ Percutaneous using external landmarks and palpation
   - ☐ Cut-down to facilitate direct visualization and access
2. Access site for endovascular repair:
   - ☐ Femoral artery
   - ☐ Brachial artery
   - ☐ Both femoral AND brachial artery
   - ☐ Other, specify type: _____
3. Did definitive repair occur during the initial endovascular procedure? ☐ Yes ☐ No
4. Was systemic anticoagulation utilized during initial endovascular repair? ☐ Yes↓ ☐ No

   If yes, list name: _____
5. Was there conversion from endovascular to open? ☐ Yes ☐ No

   If yes, answer Q2 below based on definitive open repair
6. Was aortic occlusion performed during the initial endovascular operation? ☐ Yes ☐ No

   If yes, answer AO section questions
7. Access site complication requiring operative intervention? ☐ Yes ☐ No

2. How was the major vascular injury **definitively** repaired? ☐ Open ☐ Endovascular

a. Date & Time of Initiation of Procedure: __ __/__ __/__ __ (*mm/dd/yy*) __ __: ___ ___ (*24hr Clock in hh:mm*)

leave blank if definitive repair occurred at initial procedure

b. Location of initial procedure at start: ☐ IR suite ☐ OR ☐ Hybrid OR

c. Type of surgeon at definitive repair? ☐ Trauma ☐ Vascular ☐ Thoracic ☐ IR

If definitive open repair:

1. Type of repair
   a. Primary repair: ☐ Yes ☐ No

Autologous vein interposition or bypass graft: ☐ Yes ☐ No

Synthetic graft interposition or bypass: ☐ Yes ☐ No

Other type of vascular repair: ☐ Yes↓ ☐ No

If yes, Type: _____

2. Concomitant vein injury encountered during arterial repair? ☐ Yes↓ ☐ No
   a. Repair of concomitant vein injury undertaken? ☐ Yes↓ ☐ No
      Repair lateral venorrhaphy: ☐ Yes ☐ No
      Repair interposition vein graft: ☐ Yes ☐ No
      Ligation of concomitant vein injury: ☐ Yes ☐ No
      Other type: ☐ Yes↓ ☐ No

If yes, Type: _____

3. Systemic anticoagulation utilized during definitive open repair? ☐ Yes↓ ☐ No

If yes, list name: _____

4. Need for immediate revision of intra-operative repair due to any cause? ☐ Yes ☐ No

If definitive endovascular repair :

1. Technique utilized to achieve vascular access:
   ☐ Ultra-sound guided
   ☐ Fluoroscopic guided, specify: ☐ C-arm or ☐ Fixed system
   ☐ Percutaneous using external landmarks and palpation
   ☐ Cut-down to facilitate direct visualization and access

2. Access site for endovascular repair:
   ☐ Femoral artery
   ☐ Brachial artery
   ☐ Both femoral AND brachial artery
   ☐ Other, specify type: _____

3. Definitive endovascular repair type:

   ☐ Covered stent graft repair of vascular injury
   Number of covered stents used: _____

   ☐ Bare metal stent repair of vascular injury
   Number of stents used: _____

   ☐ Coil or other material embolization
   Type of material used: _____

   ☐ Other, specify type: _____

4. Was systemic anticoagulation utilized during definitive endovascular repair?
   ☐ Yes↓ ☐ No
   If yes, list name: _____

5. Access site complication requiring operative intervention? ☐ Yes ☐ No

C. Specific Aortic Occlusion (AO) Initiation
******* This section to be completed only for AO cases*********

1. Did first AO occur at initial procedure? ☐ Yes↓ ☐ No
   If yes go to Q2
   a. Where did AO attempt take place? ☐ ED ☐ OR ☐ IR
   b. Type of AO attempted? ☐ Open ☐ Endovascular
2. Was active CPR ongoing during first AO attempt? ☐ Yes ☐ No
3. Physiology at time AO procedure initiated:
   SBP: _____ DBP: _____ HR: _____
4. Was successful AO achieved? ☐ Yes↓ ☐ No *if no go to Q5*
   a. Date & time successful aortic occlusion achieved (by balloon inflation or clamp):
   __ __ /__ __ /__ __ (mm/dd/yy) __ __:__ __ (24hr Clock in hh:mm)
   b. Within first 5 minutes after AO, what was the physiologic response?
   _____ SBP _____ DBP _____ HR
   c. Duration of AO (by balloon inflation or clamp time in minutes): _____
5. Complications of AO: ☐ Yes ☐ No
   (if Yes, answer question 4 in section F)

6a. For Open Aortic Occlusion:

1. Type of approach utilized (check one):

☐ Anterolateral thoracotomy ☐ Clamshell Thoracotomy ☐ Laparotomy

☐ Posterolateral Thoracotomy ☐ Median Sternotomy

2. Where was clamp placed? _____

6b. For Endovascular AO:

1. Technique utilized to achieve arterial access:

☐ Ultra-sound guided

☐ Fluoroscopic guided

☐ Percutaneous using external landmarks and palpation

☐ Cut-down to facilitate direct visualization and access

2. Name of type of balloon AO device utilized (check one):

☐ Coda ☐ Coda Stat ☐ Reliant ☐ Prytime ☐ Other

Specify other: _____

3. What imaging was utilized to facilitate positioning of balloon for AO?

☐ None, blind insertion using external landmarks only

☐ Ultrasound

☐ Plain film

☐ C-Arm fluoroscopy

☐ Formal angiography suite

☐ Hybrid operating or resuscitation room (THOR / RAPTOR)

4. Where was balloon deployed?

☐ Zone 1 (Origin of left subclavian artery to the celiac artery}

☐ Zone 2 (Celica artery to the lowest renal artery)

☐ Zone 3 (Lowest renal artery to the aortic bifurcation)

5. Was balloon migration observed? ☐ Yes ☐ No ☐ N/A (blind inflation)

6. Was conversion to open AO required? ☐ Yes ☐ No

D. Additional Management Information:

1. Adjunctive Medical therapy for major vascular injury? ☐ Yes↓ ☐ No

   Anti-hypertensive (beta blockade or vasodilator): ☐ Yes ☐ No

   Antiplatelet therapy (ASA, Plavix, Effient, Brillinta): ☐ Yes ☐ No

   Anticoagulation (IV or sub Q heparin): ☐ Yes ☐ No

   Other: ☐ Yes↓ ☐ No

   Type: _____

E. Definitive Hemorrhage Control:

1. Reason Initial Resuscitation Stopped:

☐ Trauma Attending and/or Anesthesiologist determined hemorrhage control achieved.
Definitive Anatomic Hemostasis Date & time: __ __ /__ __ /__ __ (mm/dd/yy) __ __:__ __ (24hr Clock in hh:mm)

☐ Further interventions were deemed futile.
Date & time declared futile: __ __/__ __/__ __ (mm/dd/yy) __ __:__ __ (24hr Clock in hh:mm)
Reasons for declaring futile:

☐ Non-survivable head injury ☐ Exsanguination ☐ Pre-injury DNR noted

☐ Blood products not available ☐ Other_____

☐ Subject expired. *(Document death on CRF Form 7)*

☐ Other (specify): _____
Date & time of other reason: __ __/__ __/__ __ (mm/dd/yy) __ __:__ __ (24hr Clock in hh:mm)

2. Location of subject at time of definitive hemorrhage control: *(Select one)*

☐ ED ☐ OR ☐ IR ☐ ICU ☐ Intermediate Level Care

☐ Nursing Unit ☐ Other, specify: _____

3. Is the patient clinically coagulopathic at the end of definitive hemorrhage control?

☐ Yes ☐ No

F. Post-operative Variables:

1. Post-operative or post-procedure therapeutic anticoagulation utilized? ☐ Yes↓ ☐ No

	Type	Start date (mm/dd/yy)	Stop date (mm/dd/yy)	Continued after discharge
☐ Yes ☐ No	Intravenous heparin	/ /	/ /	☐ Yes ☐ No
☐ Yes ☐ No	Subcutaneous LMWH	/ /	/ /	☐ Yes ☐ No
☐ Yes ☐ No	Oral warfarin	/ /	/ /	☐ Yes ☐ No
☐ Yes ☐ No	Other: Type: _____	/ /	/ /	☐ Yes ☐ No

2. Post-operative or post-procedure antiplatelet therapy? ☐ Yes↓ ☐ No

	Type	Start date (mm/dd/yy)	Stop date (mm/dd/yy)	Continued after discharge
☐ Yes ☐ No	Aspirin	/ /	/ /	☐ Yes ☐ No
☐ Yes ☐ No	Plavix	/ /	/ /	☐ Yes ☐ No
☐ Yes ☐ No	Other: Type: _____	/ /	/ /	☐ Yes ☐ No

3. Need to re-operate or re-intervene on definitive management choice during initial hospitalization? ☐ Yes↓ ☐ No

   Failure of non-operative management: ☐ Yes ☐ No

   Thrombosis of definitive vascular repair: ☐ Yes ☐ No

   Flow limiting stenosis of vascular repair: ☐ Yes ☐ No

   Pseudoaneurysm of vascular repair: ☐ Yes ☐ No

   Infection resulting in need to re-operate: ☐ Yes ☐ No

   Type of re-operation or re-intervention:

   Open operative revision: ☐ Yes ☐ No

   Endovascular revision: ☐ Yes ☐ No

   Other, specify type: _____ ☐ Yes ☐ No

4. Aortic Occlusion Complication? ☐ Yes ↓ ☐ No

Access Artery Thromboembolization: ☐ Yes ☐ No

Access Venous Thromboembolization: ☐ Yes ☐ No

Distal Limb Thromboembolization: ☐ Yes ☐ No

Thromboembolic complication at site of repair: ☐ Yes ☐ No

Form 7: Discharge/Death *(Initial Hospitalization through discharge or Day 30.)*

1. Date of hospital discharge: __ __/__ __/__ __ (mm/dd/yy) ☐ Remains Hospitalized on Day 30
2. Total (cumulative) number of ICU days: ___ ___
3. Total (cumulative) number of ventilator days: ___ ___
4. Total (cumulative) number of hospital days: ___ ___
5. Demographic Information:

   a. Gender: ☐ Male ☐ Female ☐ Unknown

   b. Age ___ ___ ___ ☐ Unknown ↓

   If age is unknown, select the age group that best describes the subjects.

   ☐ Less than 15 years of age ☐ 15 to 19
   ☐ 20 to 34 ☐ 35 to 49
   ☐ 50 to 65 ☐ > 65 years of age

   c. Ethnicity: ☐ Not Hispanic or Latino ☐ Hispanic or Latino ☐ Unknown

   d. Race: *(Check all that apply)*

   ☐ White ☐ American Indian/Alaskan Native/Aboriginal
   ☐ Asian ☐ Black/African American
   ☐ Native Hawaiian/other Pacific Islander
   ☐ Other *(Specify)*: _____
   ☐ Not Noted/Unknown

6. Was there a reported history of anti-coagulant use prior to the injury?

   ☐ Yes ↓ ☐ No ☐ Not Noted/Unknown

   ☐ Warfarin ☐ Plavix ☐ Aspirin ☐ Thrombin Inhibitors ☐ Other, specify: _____

7. Was subject discharged on therapeutic anticoagulation for vascular repair?

   ☐ Yes ↓ ☐ No ☐ Not Noted/Unknown

   ☐ Warfarin ☐ IV Heparin ☐ Sub Q Heparin ☐ Other, specify: _____

8. Was subject discharged on antiplatelet therapy?

☐ Yes ↓ ☐ No ☐ Not Noted/Unknown

☐ Plavix ☐ Aspirin ☐ Other, specify: _____

9. Subject discharged to? *(Select one)*

☐ Home ☐ Long Term Care Facility ☐ Skilled Nursing Facility

☐ Rehabilitation Facility ☐ Hospice ☐ Acute Care Hospital

☐ Other, specify: _____ ☐ Morgue

10. Did patient die? ☐ Yes ↓ ☐ No

a. Date of Death: __ __/__ __/__ __
(mm/dd/yy)

b. Time of Death: __ __:__ __
(24hr Clock in hh:mm)

c. Cause of Death: *(Check ALL that apply)*

☐ Exsanguination / Hemorrhagic Shock ☐ Traumatic Brain Injury (TBI)

☐ Respiratory/Pulmonary Contusion/Tension Pneumothorax

☐ Sepsis ☐ Multiple Organ Failure (MOF)

☐ Cardiovascular Event *(Select event(s) from below)*

○ Stroke ○ MI ○ Both Stroke & MI

☐ Pulmonary Embolism ☐ Transfusion Related Fatality

☐ Other, *(Specify)*: _____

☐ Unknown

d. Of the causes checked above, what is the primary cause of death?

☐ Exsanguination / Hemorrhagic Shock ☐ Traumatic Brain Injury (TBI)

☐ Respiratory/Pulmonary Contusion/Tension Pneumothorax

☐ Sepsis ☐ Multiple Organ Failure (MOF)

☐ Cardiovascular Event *(Select event(s) from below)*

○ Stroke ○ MI ○ Both Stroke & MI

☐ Pulmonary Embolism ☐ Transfusion Related Fatality

☐ Other, *(Specify)*: _____

☐ Unknown

11. Was a DNR ordered at any point during the hospitalization? ☐ Yes ↓ ☐ No ☐ Unknown

Date: __ __/__ __/__ __ *(mm/dd/yy)* Time: __ __:__ __ *(24hr Clock in hh:mm)*

12. Was care withdrawn at any point during the hospitalization? ☐ Yes ↓ ☐ No ☐ Unknown

Date: __ __/__ __/__ __ *(mm/dd/yy)* Time: __ __:__ __ *(24hr Clock in hh:mm)*

Form 8: Complications Check here ☐ if there are NO Complications to report.

(Record any of the following complications that occurred during the subject's hospitalization. Print additional pages as needed.)

CODE	Complication	CODE	Complication	CODE	Complication
1	Rebleeding resulting in unplanned return to OR/IR	13	Ventilator Associated Pneumonia (VAP)	25	Other Thromboembolic complication (not superficial vein thrombi)
2	Acute Kidney Injury (AKI)	14	Pneumonia (PNUI)	26	Other (specify)???
3	Acute Respiratory Distress Syndrome (ARDS)	15	Systemic Inflammatory Response (SIRS)	27	
4	Abdominal Compartment Syndrome (ACS)	16	Sepsis		
5	Open Abdominal Complications	17	Severe Sepsis		
6	Bacteremia	18	Septic Shock		
7	Catheter-Related Bloodstream Infections (CRBSI)	19	Mesenteric Thrombosis		
8	Skin Infections (SI)	20	Myocardial Infarction (MI)		
9	Soft Tissue Infection (STI)	21	Stroke or Cerebral Infarction		
10	Surgical Site Infection (SSI)	22	Deep Vein Thrombosis (DVT)		
11	Urinary Tract Infection (UTI)	23	Symptomatic Pulmonary Embolus (SPE)		
12	Multiple Organ Failure (MOF)	24	Asymptomatic Pulmonary Embolus (APE)		

↓

Code	**Start Date** *(mm/dd/yy)*	**Stop Date** *(mm/dd/yy)*	
	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown
	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown
	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown
	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown
	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown
	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown
	/ /	/ /	☐ Ongoing ☐Not Noted/Unknown

Refer to "Definitions of Complications Reported in NCTH" reference for more information.

Site P.I. Name:	Signature:

Form 9: Trauma Registry Data Form

1. Was subject data entered into the trauma registry? ☐ Yes ☐ No

2. Abbreviated Injury Scale (AIS) Score: **Check here** ☐ if the AIS Score was not noted/unknown.

ANATOMIC REGION	Head/ Neck	Face	Chest	Abdomen	Extremity	External
Score						

3. Injury Severity Score (ISS): __ __ **Check here** ☐ if the ISS Score was not noted/unknown.

Hemorrhage Control for Major Traumatic Vascular Injuries

Phase II: A Prospective Observational Study of Non-Compressible Torso Hemorrhage

Manual of Operations

Table of Contents

Chapter 1 Overview

Section 1.1: Contact Information

Houston Coordinating Center (HCC)

Principal Investigator:
John B. Holcomb, MD, FACS
Vice Chair and Professor of Surgery
Director, Center for Translational Injury Research
Jack H. Mayfield, M.D. Chair in Surgery
University of Texas Health Science Center at Houston
6410 Fannin, Suite 1100 Houston, TX, 77030
Phone: 713-500-5493
Fax: 713-512-7135
John.Holcomb@uth.tmc.edu

Co-Investigators:
Charles Wade, PhD
Professor of Surgery
University of Texas Health Science Center at Houston
Phone: 713-500-5391
Charles.E.Wade@uth.tmc.edu

Erin Fox, PhD
Assistant Professor of Surgery
University of Texas Health Science Center at Houston
Phone: 713-500-7965
Email: Erin.E.Fox@uth.tmc.edu

Stacia DeSantis, PhD
Associate Professor, School of Public Health
University of Texas Health Science Center at Houston
Phone: 713-500-9582
Email: Stacia.M.DeSantis@uth.tmc.edu

Laura Moore, MD
Associate Professor Surgery
Phone: 713-500-7244
Email: Laura.J.Moore@uth.tmc.edu

Project Manager:
Jeanette Podbielski, RN
Research Program Manager
University of Texas Health Science Center at Houston
Phone: 713-500-6407
Fax: 713-512-7135
Jeanette.M.Podbielski@uth.tmc.edu

Data Manager:
Jeff Tomasek
Research Associate
University of Texas Health Science Center at Houston
Phone: 713-500-7314
Email: Jeffrey.S.Tomasek@uth.tmc.edu

Statistician:
Thomas (Jay) Greene
Biostatistician
University of Texas Health Science Center at Houston
Phone: 713-500-9571
Email: Thomas.J.Greene@uth.tmc.edu

Senior Grant Specialist:
Donna Grayson
University of Texas Health Science Center at Houston
Phone: 713-500-5395
Email: Donna.A.Grayson@uth.tmc.edu

Administrator:
Denee Velazquez
Administrative Services Officer III
University of Texas Health Science Center at Houston
Phone: 713-500-5444
Email: Denee.Velazquez@uth.tmc.edu

Department of Defense:
Grants Officer's Representative: Wilber Malloy
Phone:
Email: Wilbur.w.malloy.civ@mail.mil

Project Officer: Jessica Clement
Phone: 301-619-4047
Email: Jessica.e.clement.ctr@mail.mil

Human Research Protection Office (HRPO):
HRPO Scientist: Derek Brown
Phone: 301-619-1667
Email: derek.t.bowden2.ctr@mail.mil

Participating Sites:

1. University of Texas Health Science Center at Houston
   PI: John Holcomb, MD
   Phone: 713-500-5493
   Email: John.Holcomb@uth.tmc.edu

   Research Coordinator: Amanda Haymaker
   Phone: 713-500-5461
   Email: Amanda.Haymaker@uth.tmc.edu

2. University of Texas Health Science Center at San Antonio
   Principal Investigator: Brian Eastridge, MD
   Phone: 210-358-0265
   Email: eastridge@uthscsa.edu

   Research Nurse: Rachelle Babbitt Jonas, RN
   Phone: 201-743-4144
   Email: babbittr@uthscsa.edu

   Research Director: Jessica Raley
   Phone: 210-743-4148
   Email: raley@uthscsa.edu

   Research Coordinator: Kristin Rocchi
   Phone: 210-743-4147
   Email: rocchi@uthscsa.edu

3. San Antonio Military Medical Center
   Principal Investigator: Valerie Sams, MD
   Phone:
   Email: valerie.g.sams.mil@mail.mil

   Co-Investigator: Kevin Chung, MD
   Phone: 210-916-3054
   Email: kevin.k.chung.mil@mail.mil

   Chief of Clinical Trials: Jamison Neilsen, MD
   Email: Jamison.s.nielsen.mil@mail.mil

   Deputy Chief of Clinical Trials: Julie Rizzo, MD
   Email: Julie.a.rizzo.mil@mail.mil

Research Nurse: Sonya Charo-Griego, RN
Phone: 201-916-9689
Email: sonya.charo-griego.civ@mail.mil

Elsa Coates, RN
Phone:
Email: elsa.a.coates.civ@mail.mil

4. Baylor College of Medicine
Principal Investigator: Ramyar Gilani, MD
Phone: 713-798-8412
Email: rgilani@bcm.edu

Co-Investigator: Rob Todd, MD
Phone: 713-798-8051
Email: SRTodd@bcm.edu

Regulatory Coordinator: Alicia Palao
Phone: 713-798-7508
Email: Alicia.Palao@bcm.edu

Study Coordinator: Reginya Knight
Phone: 713-873-5176
Email: Reginya.Knight@bcm.edu

Study Coordinator: Ava Jang
Phone: 713-798-6978
Email: Ava.Jang@bcm.edu

Grant Administrator: Malesa Jackson
Phone:
Email: mjackson@bcm.edu

1.2 DCC/Site Communication

Monthly Conference Calls

A regularly scheduled monthly meeting will be held on the 4th Tuesday of each month at 10:30 a.m. central (11:30 a.m. Eastern, 8:30 a.m. Pacific).

Monthly Site Reports

The Houston Coordinating Center will issue a monthly site report which will include enrollment and data completion updates, regulatory updates and any other information which is pertinent to the study enrollment phase.

1.3 Study Timeline

1.3.1 Overall Study Timeline

Activities	**Period 1 4/16 – 9/16**	**Period 2 10/16-9/17**	**Period 3 9/17-3/18**
Planning	✔		
Site Training	✔		
IRB approval	✔		
Enrollment		✔	
On-going Data Analysis		✔	
Study Close-out			✔

1.3.2 Subject Data Collection Timeline

ASSESSMENTS	**Pre ED**	**ED**	**Inpatient 1st 24 hrs**	**Inpatient Daily Assessment**	**Discharge Information**
Eligibility Criteria		x			
Demographics					x
Trauma Activation	x				
EMS Care	x				
Unit arrival information		x	x		
Vital Signs	x	x	x		
Glasgow Coma Scale	x	x	x		x
Life Saving Interventions	x	x	x		
Injury Information	x	x	x		
Blood Products	x	x	x		
Non-blood Fluids	x	x	x		
Procoagulant Medications	x	x	x		
Vascular Injury Information		x	x	x	
Lab Results		x	x		
Hemostasis Obtained		x	x		
Complications			x	x	x
Injury Severity Score (ISS)					x
Mortality					x
Subject Disposition					x
Past Medical History					x

Chapter 2: Recruitment/Screening/Consenting

Purpose: To clarify and standardize the procedures to be utilized to screen and enroll all eligible patients; to provide guidelines for the data collection process on all eligible subjects; and to provide background for waiver of consent.

2.1 Patient Population:

All trauma patients who meet the eligibility criteria with known or suspected NCTH admitted to one of the four participating centers.

NCTH has been defined as the presence of vascular disruption from any of the following categories: 1) Named axial torso vessel disruption, 2) Solid organ injury ≥ grade 4 (liver, kidney or spleen) with concomitant hemorrhagic shock or immediate operation, 3) Thoracic cavity injury (including lung), and 4) Pelvic fracture with ring disruption. The study procedures will identify these patients prospectively and start data collection before diagnostic testing has confirmed the diagnosis to get the most representative population of NCTH patients possible. As these conditions are often unknown at admission, data collection will commence on a wider population of patients who potentially have these injuries in order to obtain a comprehensive and representative sample of patients with NCTH.

Inclusion Criteria:

1) 15 years of age or older or ≥ 50 kg body weight if age unknown
2) Has a truncal procedure (endovascular or open) **within 4 hours** of emergency department (ED) arrival.
3) Admitted to one of four participating Level 1 trauma centers

Exclusion Criteria:

1) Prisoners, defined as those who have been directly admitted from a correctional facility

2.2 Screening Procedures:

The clinical research staff will be in-house and available on a 24/7 basis at each center to screen all subjects who are transported to the participating center and have torso hemorrhages with known or suspected non-compressible torso hemorrhage. A study ID will be assigned to each patient who meets the eligibility criteria. The clinical research staff will begin real-time data collection on all potential eligible subjects.

2.3 Data Collection Process:

For all subjects who have known or suspected torso hemorrhage, direct observation will continue until one of the following occurs:

- The patient completes the truncal procedure and arrives at a nursing unit
- The patient expires
- No surgical or endovascular procedures have occurred within the first 4 hours after ED arrival

The direct data collection will include:

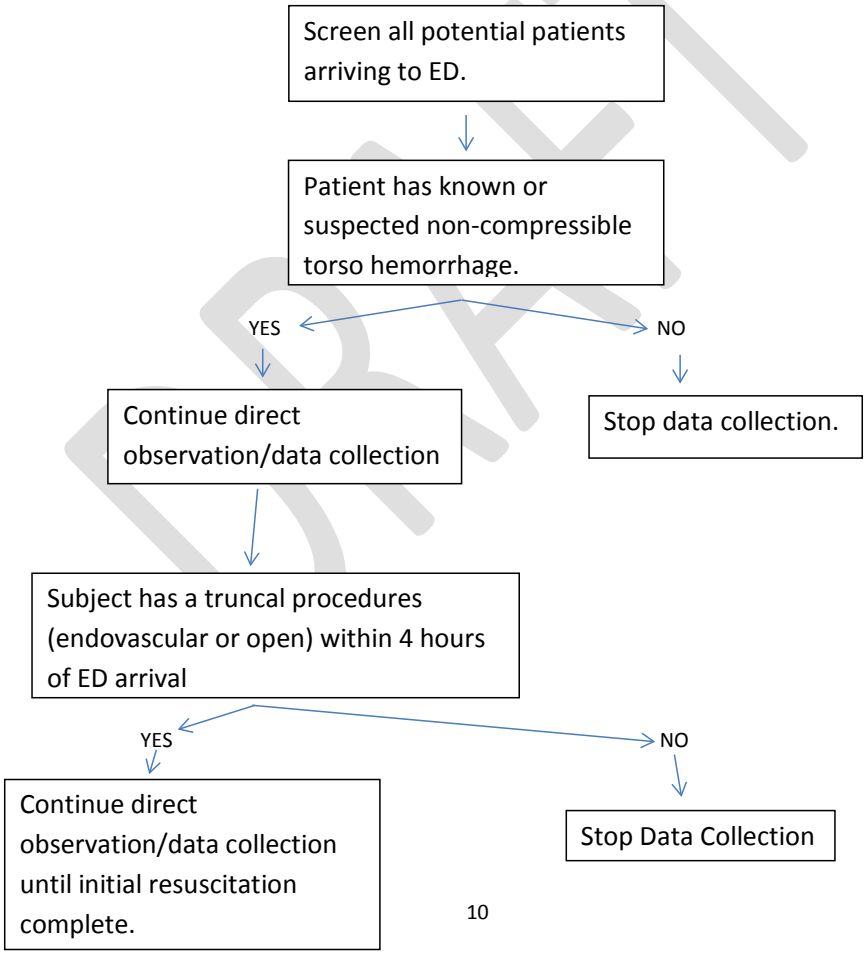
- Prehospital information obtained from the prehospital clinical staff
  (transport time, injury details LSIs, blood product and fluid usage, vital signs, hemorrhage control devices)

- In-hospital information – vital signs, LSIs, fluid and blood product usage, routine laboratory results, diagnostic procedures, interventional procedures, hemorrhage control devices, procoagulant medication and time to hemostasis.

The research staff will continue to follow the subjects through the inpatient hospital stay until time of discharge or 30 days (whichever comes first). In-hospital follow up includes interventional procedures, CT and IR images, complications, discharge status information (date/time, location, cause of death if applicable), hospital, ICU and ventilator free days, and ISS scores.

Trauma registry data will be collected on all subjects enrolled in this study.

2.4 NCTH Guidelines for Direct Observation:



Each site will be asked to provide the total number of trauma admissions on a monthly basis.

2.5 Waiver of Consent:

This study will utilize a waiver of informed consent for the following reasons:

1. The research involves no more than minimal risk – this is a prospective observational study not involving patient randomization to a treatment or intervention group.
2. The waiver will not adversely affect the rights and welfare of the patient – data regarding the standard of care procedures will be collected prospectively and there will be no contact between patient and research staff. Data collected for study purposes will be de-identified to prevent confidentiality breaches.
3. The research could not practically be carried out without waiver – this is a prospective, observational study involving no study intervention or contact with the subject.

Chapter 3: Case Report Form Completion:

Purpose: To provide guidance and instruction on how to complete the case report forms.

3.1 General Form Instructions

Study ID Numbers: A study ID # will be assigned to each eligible subject. A linking log will be kept at each site to track the study ID# with the medical record number of the subject.
Dates should be entered in MM/DD/YY format.
Times will be entered based on a 24 hour clock frame (0000 to 2359).

Form Completion:

All data must be verifiable to a source document and all changes need an audit trail. The NCTH CRF will be considered a source document for data not recorded in the subject's medical record.
Corrections will be made with a single line strikeout with the date of change and initials of person making correction.

If additional forms are needed, number the additional pages as page #.sequential number (i.e. 6.1, 6.2, 6.3).

Please refer to the following guidelines for data entry:

- All blood products will be measured in units
- All crystalloids/colloids will be measured in mLs
- Palpable diastolic B/P or HR will be recorded as palpable
- When recording the temperature, check the appropriate box for Fahrenheit or Celsius
- GCS score: The individual scores can be entered (eye movement, verbal and motor) AND/OR the total score can be entered.
- Not Detectable/Not Palpable (ND) will be recorded as -555 in REDCap
- Not Recorded/Not Done (NR) will be recorded as -666
- Unknown (UNK) will be recorded as -777
- Not Applicable (NA) will be recorded as -888

3.2 Timeline for Completion of Forms

For forms 1, 2, 3, 4, 5, and 6 will be completed and data entered within 7 to 10 working days of the time of ED admission. Form 4, the blood product and IV fluid form can be submitted as an excel spreadsheet

For forms 7 and 8 will be completed and data entered within 30 working days of the time of hospital discharge or day 30 (whichever occurred first).

For form 9 (registry information) – the form will be completed and submitted within 4 months following hospital discharge or day 30 (whichever occurred first).

3.3 Individual Case Report Form Instructions

Form 1: Verification of Eligibility/Screening

ED Arrival information – enter the date and time of patient's arrival to the ED.
Inclusion Criteria – check the "yes" or "no" box for #1 and #2. If no is checked, the patient is not eligible for the study – stop data collection.
Exclusion Criteria – check the "yes" or "no" box. If yes is checked, patient is not eligible – stop data collection.

Form 2: EMS/Pre-Hospital Care
Q1 – Date and time of injury – this is an estimated date and time.
Q2 – Date and time the air medic team was called to dispatch to scene.
Q3 – Date and time the air medic team dispatched to the scene
Q4 – Is this transport directly from scene? Check yes or no.
Q5 – Is this transport from another facility? Check yes or no.
5.a. Date and time of arrival to first facility.
5.b. Date and time of departure from first facility.
5.c. Indicate type of facility
**For the prehospital medic team dates/times, use the times recorded on the run sheets.
Q6 – Check the mode of transport.
Q7 – Enter first available vital signs and GCS score for the EMS transporting patient to final receiving hospital (your institution).
Q8 – Check all boxes that apply for both blunt and penetrating. The subject may have more than one cause in blunt, penetrating or both.
Q9 – Check all boxes that apply for prehospital lifesaving interventions (Including those at transferring facility)

***** For blood products and IV fluids given prehospital, enter the type and amounts on form 4.**
***** For procoagulants given prehospital, enter the type and amounts on form 5.**

Form 3: Initial 24 hour Vital Signs and Glasgow Coma Scale (GCS) Score
******* This form will collect the first available vital signs and GCS score at the **time of ED arrival**.

Do not record the pre-hospital vital signs & GCS score here. The pre-hospital vital signs should be recorded on form 2 only.

Enter the first available vital signs and GCS upon arrival to the ED.

Reminder:
For the temperature box, check the correct box for Fahrenheit or Celsius.

If an admission TEG was done, please check the box denoting what type the test was: Rapid or Kaolin. If it was a Rapid TEG, please enter the ACT value. If it was a Kaolin TEG, please enter the R-time value. Then, please enter the remaining TEG parameters.

Form 4: IV Fluids and Blood Products Transfusion Record

IV fluids and blood products will be captured for the 1st 24 hours after ED admission only, including any prehospital fluids or products.
Enter the location code, blood/fluid code, start date, start time, amount and units.

If "other" was selected for location, blood product, crystalloid or colloid, please specify in the table in the appropriate column.

For those subjects who are followed with direct observation, the direct observation will continue until initial resuscitation has been achieved. The research staff should continue to monitor the subject's status frequently (every 1 to 2 hours) through the 24 hour period to capture additional fluids/blood products and other interventions.

For clarification, 1 unit of platelets = 6 pack of platelets; a unit of jumbo plasma = 2 units. Once a bag/product is spiked and hung, it is considered 1 unit (even if the whole bag is not given).

Form 5: Procoagulant Medications
Procoagulant medications will be recorded for the 1st 24 hours after ED admission, including any prehospital administration.
Enter the location code, start date, start time and medication code.
If "other" was selected for location or medication, please specify in the table in the appropriate column.

Form 6: Vascular Injury Information
Box – Please check all arteries, veins and solid organs injured.
Q1 – Please note what the primary source of bleeding was for all veins injured.
Q2 – Please note what the primary source of bleeding was for all arteries injured.
Q3 – Finally, of all the injuries checked, select the primary source of bleeding.

Section A
Provide answers for questions 1 and 2.
Section B
Q1 – Choose how the major vascular injury was repaired INITIALLY and record the date/time of start of procedure, location and type of surgeon performing procedure (Q1a – Q1c)
***If initial management was open, answer the 4 questions concerning initial open management and skip the 7 questions concerning initial endovascular management.
*** If initial management was endovascular, skip the 4 questions concerning initial open management and answer the 7 questions concerning initial endovascular management. If, after completing the 7 questions, there was conversion from endovascular to open repair, proceed to Q2 and answer the questions based on the definitive open repair.
If aortic occlusion (AO) was performed in the initial management, fill out question set in section C.

Q2 – Choose how the major vascular injury was repaired DEFINITIVELY and record the date/time of start of procedure, location and type of surgeon performing procedure (Q2a – Q2c).
***If definitive repair was open, answer the 4 questions concerning definitive open repair and skip the 5 questions concerning definitive endovascular repair.

Commented [TJS1]: Whatif there was conversion from endovascular to open? Do we want them to then also fill out the open initial management or will the definitive open in Q2 cover this?
Yes

So is it yes – fill out open initial also or, yes – continue to open definitive?

Fixed. Does it read right now?

*** If definitive repair was endovascular, skip the 4 questions concerning definitive open repair and answer the 5 questions concerning definitive endovascular repair.

Section C
If AO was performed during the treatment, please fill this section out.
Q1 – If first AO occurred at the initial procedure (see above section B, question 1), check "yes", skip Q1a and Q1b, and proceed to answer remaining questions 2-6 of this section. If first AO did not occur at the initial procedure, check "no", answer Q1a and Q1b, and then answer remaining questions 2-6.
Q4 – If AO was successfully achieved, then provide date/time, vitals and duration of AO (Q4a – Q4c).
Q5 – If there were any complications, please answer yes and record them in section F Q4.
Q6 – If open AO was performed, only fill out Q6a (Q6a1 & Q6a2). If endovascular AO was performed, only fill out Q6b (Q6b1 – Q6b6). If there was conversion from endovascular AO to open AO (Q6b6 = "yes"), fill out Q6a (open AO) also.

Section D
Q1 – If there was adjunctive medical therapy for the vascular injury, please check the box of the medication given or provide the name of the medication given if different from choices.

Section E
Q1 – Please communicate with the trauma surgeon performing the operation or procedure and anesthesiologist to determine the reason initial resuscitation stopped:
*if hemorrhage control was achieved (surgeon declares hemostasis based on the following criteria: a) no bleeding requiring intervention in the surgical field or b) in the IR suite, resolution of blush after embolization) – provide date and time
*if further interventions were deemed futile – provide date, time and reason(s)
*if subject expired – document on Form 7
*if other reason – specify and provide date and time.
Q2 – Mark the location of subject at the time of definitive hemorrhage control.
Q3 – Is patient clinically coagulopathic at the end of hemorrhage control? Clinically coagulopathic is defined as bleeding from injured surfaces not controlled by sutures or from uninjured sites. Please communicate with the trauma surgeon or attending to determine this and check yes or no.

Section F
Q1 – Was post-operative or post-procedure therapeutic anticoagulation utilized? If yes, answer fields in the table after the question. If no, go to Q2.
Q2 – Was post-operative or post-procedure antiplatelet therapy utilized? If yes, answer fields in the table after the question. If no, go to Q3.
Q3 – Was there a need to re-operate or re-intervene on definitive management choice during initial hospitalization? If yes, answer the next 5 questions and indicate the type of re-operation or re-intervention.
Q4 – Was there an aortic occlusion complication? If yes, please answer the next 4 questions.

Form 7: Discharge/Death
Q1 – Enter date of hospital discharge or check the box if the subject remains hospitalized 30 days after

Commented [TJS2]: Q1 needs to be looked at…confused if 1a and 1b are answered if Q1 answer is Y or N. Good catch should be for yes.

Fixed. Does it read right now?

Commented [TJS3]: What if there was conversion to open AO, will we want them to also fill out the open AO Q6a? yes

Fixed. Does it read right now?

Commented [TJS4]: This needs to be updated on CRF

Fixed on CRF.

admission to the ED.
Q2 – Enter the total number of ICU days. Note this is cumulative so if the patient was discharged and readmitted to the ICU, count all days in the ICU up to day 30.
Q3 – Enter the total number of ventilator days. Note this is cumulative so if the patient was extubated and reintubated, count all days the subject was intubated up to day 30.
Q4 – Enter the total number of hospital days.
Q5 – Enter the demographic data – gender, age, ethnicity and race.
Q6 – Complete information if available regarding history of anti-coagulation medication prior to injury.
Q7 – Complete information regarding use of therapeutic anti-coagulation medication at time of discharge.
Q8 – Complete information regarding use of antiplatelet therapy at time of discharge.
Q9 – Select the location subject was discharged to. If other is selected, please enter location in text box.
Q10 – Did patient die – if yes, check "yes" and complete 10a-10d.
Q10a – Enter date of death (if applicable)
Q10b ~~*11*~~ – Enter time of death (if applicable)
Q10c – Check all causes of death. Refer to section 5.2 Causes of Death Definitions.
Q10d – Of the causes checked in Q10c, the PI must select the primary cause of death. In the event the PI cannot decide on the primary cause, contact the CCC for assistance.
*** Note: Withdrawal of care is not considered a cause of death.
Q11 – DNR during hospital – check the yes or no box. If yes, complete date and time for the time DNR was ordered.
Q12 – Care withdrawn- if yes, complete date and time for the time care withdrawn.
~~*Q14* – Check all causes of death. Refer to section 5.2 Causes of Death Definitions.~~
~~*Q15* – Of the causes checked in Q 14, the PI must select the primary cause of death. In the event the PI cannot decide on the primary cause, contact the CCC for assistance.~~
~~*** Note: Withdrawal of care is not considered a cause of death.~~

Form 8: Complications
Record complications which occurred through the hospitalization or up to day 30, whichever comes first. Refer to section 5.1 for the definitions for each complication identified on this form. For each complication, enter the complication code, start date, stop date and whether the complication is ongoing or not noted/unknown. At the time of completion of this form, the PI will be required to sign off that they have reviewed the list of complications.

Form 9: Trauma Registry Data Form
Complete the AIS and ISS scores on this form.

3.5 Data Queries
Multiple range checks for values are imbedded within each of the forms listed to allow for concurrent data entry checks. After data entry on the form has been completed (and indicated by the "marked complete" submission) the form will be integrated into additional checks involving validations across forms, "other" text fields evaluated and missing data. These listings (by subject id and form) will be sent to the coordinators on a weekly basis for correction.

Chapter 4: Trauma Registry Information
Purpose: To provide guidance on accessing data from the trauma registry and instructions on how to submit the data to the HCC.

The trauma registries will be asked to assist with the information routinely entered into the NTDB. Additional information regarding specific data elements to be collected will follow as the study proceeds.

Chapter 5: Safety Monitoring

Purpose: To provide definitions on the complications to be monitored and collected for the study; to provide definitions for the cause of death to be used by the local PI; and to provide instruction on how to complete the death adjudication form and what ancillary documents are required for the adjudication process.

5.1 Complication Definitions

Refer to the following list of complications which will be collected on all "highest risk" subjects during the initial hospitalization or up to 30 days. Document each incidence of the complications on Form 8.

1. Rebleeding resulting in unplanned return to OR and/or IR

2. Abdominal Compartment Syndrome (ACS)

Elevated intra-abdominal pressure (> 20 cm H2O) requiring the opening of the abdominal cavity with at least one of the following: 1) oliguria (<30cc/hr), 2) diminished cardiac output (< 2.5 L/min/m2), 3) elevated static airway pressures (> 45 cm H2O), or 4) PaO2/FiO2 ratio of less than 200. *(TRDB, 2007)*

3. Abdominal Complications (Open or Closed) after Exploratory Laparotomy

Abdominal complications include:

a. Fistula – abnormal connection between two epithelial-lined organs that normally do not connect.
b. Abscess of other evidence of any infection involving the intra-abdominal or retroperitoneal contents is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
c. Other (please specify)

4. Acute Kidney Injury (AKI) / Acute Renal Failure

Rapid loss of kidney function (within any 48 hours), measured by a rise in creatinine (increase in serum creatinine of either an absolute count of >/= 0.3 mg/dl or 50% increase), decrease in the GFR (> 25%) and/or reduction in urine output defined as <0.5 ml/kg/hr for at least 6 hours.
(Acute Kidney Injury Network, 2007)

5. Acute Respiratory Distress Syndrome (ARDS)-

Lung injury characterized by hypoxemia, pulmonary edema, low lung compliance and capillary leakage. The following criteria must be met:

1. Timing – within 1 week of a known clinical insult or new or worsening respiratory symptoms.
2. Chest Imaging – Bilateral opacities – not fully explained by effusions, lobar/lung collapse or nodules
3. Origin of edema – Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assess (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present
4. Oxygenation
   A. Mild – 200 mmHg < PaO2/FIO2 </= 300 mmHg with PEEP or CPAP >/= 5 cmH2O[c]

B. Moderate – 100 mmHg < PaO2/FIO2 </= 200 mmHg with PEEP or CPAP >/= 5 cmH2O[c]
C. Severe - PaO2/FIO2 < 100 mmHg with PEEP >/= 5 cmH2O[c]

6. Cardiac Arrest
Sudden cessation of cardiac activity (Includes pulseless electrical activity [PEA]).
(TRDB, 2007)

7. Empyema (EMP)
The presence of pus, a positive Gram stain or culture of pleural fluid, or a pleural fluid pH under 7.2 with normal peripheral blood pH. (*American Journal of Medicine 2006, 119(10): 877-83*)

8. Infections

a. **Bacteremia**
The presence of viable bacteria in the blood with positive blood cultures.
(American College of Chest Physicians/Society of Critical Care Medicine, 1992)

b. **Catheter-Related Bloodstream Infections (CRBSI)**
The presence of bacteremia/fungemia in a patient with a central venous catheter (CVC) in which there is no alternate source for bacteremia/fungemia except the catheter. To diagnose CRBSI, the patient must have clinical manifestations of infection (fever, chills or hypotension); a positive blood culture from a peripheral vein; and some microbiologic evidence the catheter is infected.
Diagnostic criteria (all of 1, 2 and 3 must be met within a 48 hr period):
1. A single positive blood culture from a peripheral vein
2. Clinical manifestations of infection including at least one of a, b, or c
   a) Fever >38.5C
   b) WBC >10,000 or < 3000 per cubic millimeter
   c) Hypotension (SBP < 90) or > 25% drop in systolic blood pressure
3. Microbiologic evidence of catheter infection (at least one of a, b, c, or d)
   a) positive semiquantitative (>15CFU/catheter segment) culture in which the same organisms isolated from the catheter and peripheral blood (**this is the most commonly used technique)**
   b) positive quantitative (>103CFU/catheter segment catheter) culture in which the same organism is isolated from the catheter and peripheral blood
   c) simultaneous quantitative blood cultures with a > 5:1ratio of bacteria (CVC versus peripheral)
   d) differential period of central venous catheter culture versus peripheral blood culture positivity of > 2 hours *(TRDB, 2007)*

c. **Skin Infection (SI)**
Skin infections must meet at least 1 of the following criteria:
1. Patient has purulent drainage, pustules, vesicles, or boils.
2. Patient has at least 2 of the following signs or symptoms with no other recognized cause: pain or tenderness, localized swelling, redness, or heat and at least 1 of the following:
a. organisms cultured from aspirate or drainage from affected site; if organisms are normal skin flora (i.e., diphtheroids [Corynebacterium spp], Bacillus [not B anthracis] spp, Propionibacterium spp, coagulase-negative staphylococci [including S epidermidis], viridans group streptococci, Aerococcus spp, Micrococcus spp), they must be a pure culture
b. organisms cultured from blood

c. positive laboratory test performed on infected tissue or blood (e.g., antigen tests for herpes simplex, varicella zoster, H influenzae, or N meningitidis)
d. multinucleated giant cells seen on microscopic examination of affected tissue
e. diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen.
CDC/NHSN Surveillance Definitions for Specific Types of Infections, January 2014

d. **Soft Tissue Infection (STI)**

Soft tissue infections include necrotizing fascitis, infectious gangrene, necrotizing cellulitis, infectious myositis, lymphadenitis, or lymphangitis and must meet at 1 of the following criteria:
Patient has organisms cultured from tissue or drainage from affected site.
2. Patient has purulent drainage at affected site.
3. Patient has an abscess or other evidence of infection seen during an invasive procedure or histopathologic examination.
4. Patient has at least 2 of the following signs or symptoms at the affected site with no other recognized cause: localized pain or tenderness, redness, swelling, or heat
and at least 1 of the following:
a. organisms cultured from blood
b. positive laboratory test performed on blood or urine (e.g., antigen tests for H influenzae, S pneumoniae, N meningitidis, Group B Streptococcus, or Candida spp)
c. diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen.
CDC/NHSN Surveillance Definitions for Specific Types of Infections, January 2014

e. **Surgical Site Infections (SSI)**

- *Superficial Incisional/Wound Infections*

Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision **and at least one** of the following:
1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.
(TRDB, 2007)

- *Deep Incisional SSI*

Infection occurs within 30 days after the operation and the infection appears to be related to the operation *and* infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision ***and*** at least ***one*** of the following:
1. Purulent drainage from the deep incision, but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38ºC), localized pain or tenderness, unless site is culture-negative
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

- *Organ/Space SSI*

Infection occurs within 30 days after the operation and the infection appears to be related to the

operation *and* infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation ***and*** at least ***one*** of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space (if the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth.)
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

(TRDB, 2007)

f. **Urinary Tract Infection (UTI)**

Must meet at least 1 of the following criteria:

At least one of the following signs/symptoms:

- Fever (>38º C)
- Suprapubic tenderness
- Costovertibral angle pain or tenderness

And

A positive urine culture of ≥105 colony-forming units (CFU)/ml with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements.

CDC/NHSN Surveillance Definitions for Specific Types of Infections, January 2014

9. Multiple Organ Failure (MOF)

Multiple organ failure will be defined using the Denver Multiple Organ Failure (MOF) scoring system. This system evaluates four organ systems: pulmonary, hepatic, renal, and cardiac. Organ dysfunction is graded on a scale from 0 to

The pulmonary score is determined by the PaO2/FiO2 (P/F) ratio. P/F >208 receive zero (0) points, ratios of 208-165 receive 1 point, 165-83 receive 2 points, and 83 receive 3 points.

The renal system is graded by serum creatinine level in mg/dL: 0 points for <1.8, 1 point for 1.8-2.5, 2 points for 2.5-5.0, and 3 points for >5.0 mg/dL.

The hepatic score is calculated by total serum bilirubin level in mg/dL: 0 points for bilirubin <2.0, 1 point for 2.0-4.0, 2 points for 4.0-8.0, and 3 points for bilirubin >8.0 mg/dL.

Cardiac dysfunction is graded based on inotropic support and cardiac index (C.I.). No inotropes and cardiac index >3.0 L/min per meter squared yield a score of zero (0), whereas minimal inotropic support or C.I. <3.0 yield a score of 1. Moderate and high dose inotropic receive scores of 2 and 3, respectively.

Scores not recorded are assumed to be normal and calculated as zero (0).

****For multiple organ failure, the MOF score is calculated as the sum of the simultaneously obtained individual organ scores on each hospital day. Single system organ failure is defined as an organ failure grade >0. MOF is defined as a total score of 4 or greater.

10. Pneumonia (PNUI)

Pneumonia must meet at least one of the following:

1. Fever (>38°C or >100.4°F)
2. Leukopenia (<4000 WBC/mm3) or leukocytosis (≥12,000 WBC/mm3)
3. For adults ≥70 years old, altered mental status with no other recognized cause and at least two of the following:

1. New onset of purulent sputum, or change in character of sputum or increased respiratory secretions, or increased suctioning requirements
2. New onset or worsening cough, or dyspnea, or tachypnea
3. Rales or bronchial breath sounds
4. Worsening gas exchange (e.g., O2 desaturations (e.g., PaO2/FiO2 ≤240), increased oxygen requirements, or increased ventilator demand)

CDC/NHSN Surveillance Definitions for Specific Types of Infections, January 2014

11. Sepsis

A systemic response to infection. Two or more of the following three conditions must be present: (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or PaC02<32 mmHg; and white blood cell count >12,000/cu mm,<4,000/cu mm, or> 10% immature (band) forms; AND a known or suspected infection confirmed by culture, CXR, or CT.
(American College of Chest Physicians/Society of Critical Care Medicine, 1992)

12. Severe Sepsis

Severe sepsis is defined as SIRS plus infection plus acute organ dysfunction. Type of acute organ dysfunction are as follows:
Neurologic: GCS score < 13 on recognition of sepsis or deteriorating GCS score to < 13 during first 24 hours.
Pulmonary: PaO2/FiO2 ratio < 250 (<200 if lung is the primary site of infection) and pulmonary capillary wedge pressure (PCWP) not suggestive of fluid overload
Renal (one of the following): Urine output < 0.5 mL/kg for ≥ 1 hour despite adequate volume resuscitation or increase in serum creatinine ≥ 0.5 mg/dL from baseline (measured with 24 hours of starting sepsis resuscitation). Adequate volume resuscitation is defined as a minimum intravenous fluid infusion of 20 mL/kg/ideal body weight or central venous pressure ≥ 8 mm Hg or PCWP ≥12 mm Hg
Coagulation (one of the following): INR > 1.5, platelet count <80,000 or ≥ 50% decrease in platelets compared with 24 hours after starting sepsis resuscitation in the absence of chronic liver disease
Hypoperfusion: lactate > 4 mmol/L
Journal of Trauma, Volume 70, Number 3, March 2011

13. Septic Shock

Septic shock is defined as SIRS plus infection plus acute cardiac dysfunction that is defined as:

1. IV fluid challenge ≥ 20 mL/kg/ideal body weight of isotonic crystalloid infusion or CVP ≥ 8 mm Hg or PCWP ≥ 12 mm HG

AND

2. Requirement of vasopressors to increase MAP ≥ 65 mm Hg.

Journal of Trauma, Volume 70, Number 3, March 2011

14. Systemic Inflammatory Response Syndrome (SIRS)
SIRS is a serious condition related to systemic inflammation, organ dysfunction, and organ failure. It is a subset of cytokine storm, in which there is abnormal regulation of various cytokines. Two or more of the following must be present for SIRS (without a positive culture): 1) temperature below 36° C or above 38° C, 2) heart rate > 90 bpm, 3) > 20 breaths per minute or, on blood gas, a PaCO2 less than 32 mmHg, 4) WBC < 4,000 cells/mm3 or > 12,000 cells/mm3. *(American College of Chest Physicians/Society of Critical Care Medicine, 1992)*

15. Thromboembolic complications
g. **Myocardial Infarction (MI)**
Acute, irreversible myocardial injury documented by both of: (1) Abnormal increase in CK-MB ortroponin and (2) New, serial T-wave, S-T segment or Q wave ECG abnormalities. *(TRDB, 2007*
h. **Stroke or Cerebral Infarction.** New neurological deficit not present on admission which is: 1) sudden or rapid in onset, and 2) lasts >24 hours and 3) confirmed as an acute infarction by CT or MRI and 4) that is consistent with the physical exam. *(TRDB, 2007)*
i. **Deep Vein Thrombosis (DVT)** – venous thrombosis confirmed by autopsy, venogram, duplex or other non-invasive vascular evaluation. Document whether the DVT is symptomatic or not
j. **Pulmonary Embolus (PE)** A clinically significant (resulting in hypoxia or tachycardia or hypotension) blood clot lodged in the lumen of a pulmonary artery as diagnosed by CT angiogram, pulmonary angiogram or ventilation perfusion scan. To be differentiated from occult, non-clinically significant PE. *(ROC Hypertonic Resuscitation MOO, 2008)*
k. **Mesenteric Thrombosis** (arterial or venous) Documented on arteriogram, CT angiogram, operative findings or autopsy
l. **Other (not superficial vein thrombi)**

16. Ventilator Associated Pneumonia (VAP)
Pneumonia in patients who have been mechanically ventilated for > 48 hours.
Criteria a-c must be satisfied within a 48 hr period:
a) Radiologic criteria:
i. New radiographic infiltrate that persists for at least 24 hours not associated with ALI, ARDS, pulmonary contusion, TRALI or TACO.
b) Clinical criteria (one of i or ii)
i. Tm> 38.5°C or <35.0°C
ii. WBC> 12,000 or <4000 per cubic millimeter
c) Bacterial confirmation by at least one of:
i. Quantitative microbiologic cultures obtained by bronchoalveolar lavage yielding≥10^4colony forming units [CFU]/ml or protected specimen brush>10^3 CFU/ml (preferred diagnostic method)
ii. Histopathologic exam of lung tissue shows one of a or b:
(a). Abscess formation with intense PMN accumulation in bronchioles &alveoli. (b). Quantitative culture of lung parenchyma that shows $\geq$ 10^4cfu/g tissue.
iii. Positive blood culture for bacterial pathogen identified in sputum or respiratory culture

iv. Positive pleural fluid culture with same organism identified in sputum or other respiratory cultures
v. Positive sputum gram stain with ≥3+ of one type of pathogenic bacteria
vi. Heavy or moderate growth of one type of pathogenic bacteria on semi-quantitative sputum culture

(TRDB, 2007)

5.2 Cause of Death Definitions

This information will be entered on Form 11. There are 2 parts to Question #17 on Form 11 regarding the cause of death. The first question will ask to document ALL causes of death. The second question will ask for the PRIMARY cause of death.
Refer to the following list to document the cause of death.

1) **Exsanguination / Hemorrhagic Shock**
Exsanguination: death caused by uncontrolled bleeding.
Hemorrhagic Shock: shock associated with the sudden and rapid loss of significant amounts of blood. Severe traumatic injuries often cause such blood losses. This results in inadequate perfusion to meet the metabolic demands of cellular function. Hemorrhagic death occurs within a relatively short time (usually during active resuscitation) after admission unless transfusion quickly restores normal blood volume. Occasionally rebleeding may occur, resulting in later deaths.

2) **Traumatic Brain Injury (TBI)**
An injury to the brain caused by penetration of the skull or movement of the brain within the skull. TBI as a cause of death usually occurs with several days of admission. TBI death is directly related to: (1) a TBI deemed non-survivable and documented as such by a faculty physician; (2) rapid deterioration and cardiovascular collapse following hemodynamic changes consistent with herniation, or (3) brain death.

3) **Respiratory/Pulmonary Contusion/Tension Pneumothorax**
Respiratory: any loss of ventilatory capability, usually from a mechanical issue somewhere between the ventilator and the pulmonary parenchyma.
Pulmonary contusion: injury to lung parenchyma, leading to edema and blood collecting in alveolar spaces and loss of normal lung structure & function. This lung injury develops over the course of 24 hours, leading to poor gas exchange, increased pulmonary vascular resistance and decreased lung compliance. Usually death will occur within hours of injury. (MedicineNet.com)
Tension Pneumothorax: The accumulation of air under pressure in the pleural space causing death within minutes. (MedicineNet.com)

4) **Sepsis** – An overwhelming systemic response to documented infection. Patients dying of sepsis usually do so > 72 hours after admission.

5) **MOF** – Altered organ function in at least 2 organ systems. Progressive and profound organ dysfunction that is incompatible with life. Patients dying of MOF usually do so > 48 hours after admission.

6) Stroke
New neurological deficit not present prior to injury which is sudden or rapid in onset, lasts > 24 hours and is confirmed as an infarction by CT or MRI, acutely causing death. (TRDB, 2007)

7) **Myocardial Infarction**

Acute, irreversible myocardial injury documented by both: (1) Abnormal increase in CK-MB or troponin and (2) New, serial T-wave, S-T segment or Q wave ECG abnormalities acutely causing death. (TRDB, 2007)
8) **Pulmonary Embolism** - A blood clot lodged in the lumen of a pulmonary artery acutely causing death, diagnosed by CT angiogram, pulmonary angiogram or ventilation perfusion scan. (TRDB, 2007)

9) **Transfusion Related Fatality** – fatality as a direct result of a complication of blood component transfusion. Refer to the 13 transfusion related complications. (Practice Guidelines for Blood Transfusion) Do we need to keep those in the complication list?
10) **Other (specify)**
11) **Unknown**

5.3 Death Adjudication Process
Similar to PROPPR, it is expected that patients enrolled in NCTH will have a significant mortality rate. It is likely that subjects will have multiple causes of death, especially those that occur after 72 hours. We require that site PI's and study coordinator's discuss each death and use the following categories to assign causality. At the time of death, please place the subject into the death category and describe those proximate clinical issues most likely to have contributed to death.

In the event of a subject death, the local site PI will determine the cause of death using the categories mentioned above in Section 5.2. The cause of death will then be forwarded to the HCC for review. Timing of the withdrawal of care (as applicable) will be noted in the assessment.

Redacted records will be sent to the HCC to facilitate accurate death reconciliation. These records include: 1st 24 hour operative notes, anesthesia records and CT scan reports, admission HX and physical, discharge summary, death summary and autopsy reports and any other important supporting documents from the site PI. Please submit a short paragraph within 2 weeks of the death (from the site PI) summarizing the data supporting the final cause(s) of death.

The HCC PI will review the cause of death assessment and redacted subject records. The HCC PI will then determine cause of death based on the available information. If the HCC PI and the local PI are in agreement of the cause of death, no further action will be necessary. In the event there is a difference in the cause of death, the HCC PI will contact the local PI and further discuss the scenario and ask for additional redacted information as needed.

5.4 Monitored Site Visits
The HCC will monitor the data entered into RedCap on a regular basis and will contact the site coordinator via email and/or telephone as needed to address questions. The HCC staff will also be available to go out to the sites as needed if there are issues with the data collection/entry process that require in person monitoring and/or additional training or if the site personnel request an in person site visit.

Chapter 6: Patient and Data Confidentiality
Purpose: To provide information on the responsibilities of maintaining patient confidentiality on all study levels (HCC, site and communication between the HCC & sites).

HCC Responsibilities
All HCC staff handling sensitive NCTH records and data are responsible for adhering to the procedures described herein. The HCC PI, Biostatisticians data management staff have access to the entire database, including sensitive information. The HCC team will work to ensure that data produced for reports or datasets, had been de-identified and blinded.

Site Responsibilities:
The research staff at each site will follow their local university/institution's HIPPA policies and procedures to ensure all measures are taken to protect the subject's confidentiality.

The HCC will receive only information that has been de-identified.

All NCTH Study Related Personnel (HCC and site)
To ensure all measures are taken to comply with the HIPPA guidelines, refer to the following guidelines:
Sensitive records and data include the following:

- Management information concerning workload, performance, staffing, and similar data.
- Correspondence and documents, which must be protected from unauthorized alteration or disclosure. These types of data include all correspondence, memoranda, and other documents whose release or distribution outside the HDCC needs to be controlled.
- Clinical trial data.
- Payment information that is used to authorize or make cash payments to individuals or organizations.
- Proprietary study related information that has value in and of itself must be protected from unauthorized disclosure.
- Correspondence and documents that are considered highly sensitive and/or critical to an organization and must be protected from unauthorized alteration and/or premature disclosure.
- Records subject to the Privacy Act, which contain information that meets the qualifications for Exemption 6 of the Freedom of Information Act, i.e., for which unauthorized disclosure would constitute a "clearly unwarranted invasion of personal privacy" likely to lead to specific detrimental consequences for the individual in terms of financial, medical, psychological, or social standing.

Computers, Fax Machines and Printers
Computers, fax machines and printers that may be used for confidential data shall be placed in secure areas where access is restricted to only those individuals with permission to access confidential information.

Sensitive electronic data will be stored on a designated secure server. Storing data on workstations will be minimized wherever possible and deleted immediately.

Computer Display
Staff will remove confidential data from screens where it is not required.

Staff will need to be aware of the position of computer screens. Unauthorized individuals should not be able to read screens containing confidential information. Use a monitor visor or hood in service areas.

Staff will need to log off from applications that show confidential data so that no data is accessible after you are finished.

Computers that are used to access confidential data will have screen savers so that unauthorized people cannot read the information if they happen to wander into a restricted area.

Computers that are used to access confidential data will have a time-out feature so that when a staff person steps away from his/her computer for a period of time, the staff person is required to re-enter his or her password. Computers that are used to access confidential data must be password protected.

Employees should only be given access to those computers and information to which they are entitled. Each employee must use his/her own user name and password to access computers containing confidential data.

Telephone, Internet (email) and Other Communications
References to any subject in the NCTH trial will include only the study ID number. Subject names are considered PHI and should not be used. Staff will not verify a study subject by any identifier other than their study ID.

Paper
Paper records and reports containing PHI will not be left in locations where non-NCTH staff (or others without authority to view the information) have access to that information such as printers or unattended on a desktop in open view. Reports which are no longer needed and contain confidential and/or sensitive data must be shredded or stored securely in a locked file cabinet until they can be shredded.

Laptops and PDAs
Laptops or other portable devices (PDA's, etc.) should not be used to store confidential information.

Laptops and other portable equipment (PDAs, travel drives, CD/DVDs, etc.) that contain confidential information must be kept secure and able to be accessed only by authorized individuals. Staff will delete confidential information from laptops and personal devices as soon as it is no longer needed on those devices.

Chapter 7: Site Activity Reports
Purpose: To provide an outline on sending invoices for payments and to provide instruction on the annual reporting requirements.

7.1 Invoicing Requirements

Subcontracts between UTHealth and the participating clinical sites indicate that UTHealth will reimburse each subcontractor for the direct and indirect costs incurred in the performance of tasks outlined in the scope of work found in the subcontract. The total costs cannot exceed the estimated cost that is provided in each subcontract.

All subcontractors should submit invoices at least quarterly and no more than monthly to UTHealth at the following address:

POST AWARD FINANCE
The University of Texas Health Science Center at Houston
7000 Fannin, UCT 902
Houston, Texas 77030-1500

Invoices should be submitted:

- using the standard invoice shown at the end of this section
- prepared on institutional letterhead
- certify that all payments requires are for appropriate purposes
- state the period for which reimbursement is being requested
- itemize the costs by the following budget categories:
    - Salaries
    - Employee Benefits
    - Equipment
    - Consultant Costs
    - Travel
    - Other Direct Costs
    - Total Direct Costs
    - Indirect Costs
    - Total
- show current costs and cumulative costs to date
- include subaward number
- signed by Subcontractors authorized representative

Yearly final invoices are due no later than 30 days following termination (i.e., September 14), and it must be signed and marked “Final.” In addition, the final invoice should include the following statement:

> "The Subcontractor assures to the University that all expenditures were incurred in full compliance with OMB Circular A-133 or its own applicable audit regulations. Disallowed costs if found during the retention period of this Subcontract will be promptly refunded to University."

If a finding or questioned cost is found related directly to this Subcontract, then the Subcontractor will promptly notify UTHealth in order to proceed with resolution of such matter, as may be required by UTHealth's prime sponsor or applicable Federal regulations.

The following expenditures require prior approval of the UTHealth Director of Contracts, Sponsored Projects Administration, or designee:

1. A 25% reduction in time devoted to the project by the Principal Investigator or Project Director.
2. Items of general purpose equipment, e.g., office equipment and furnishings, air conditioning, reproduction equipment, automatic data processing equipment, etc.
3. Individual items of equipment costing $5,000 or more. All such items identified in the budget attachment are automatically approved for acquisition.
4. The subaward, transfer or contracting out of any work except for routine purchase of supplies, materials, equipment or general support services.

Sample Invoice

Attachment 6
Sample Invoice

COLLABORATOR:_____ Date: _____

PAYMENT ADDRESS:
_____
_____
_____
_____

INVOICE NO. _____
PRIME AWARD NO. _____
SUBAWARD NO. _____
AWARD AMOUNT $_____

Billing Period:

_____ to _____

Submit invoice to:
Post Award Finance
The University of Texas Health
Science Center at Houston
7000 Fannin, UCT 902
Houston, Texas 77030-1500

Description/Cost Items	Amt Billed for Current Period From: To:	Cumulative Amt from Inception From: To:
Personnel		
Consultant costs		
Equipment		
Materials and Supplies		
Travel		
Other Direct costs		
IDC Exclusions		
Indirect cost		
Total costs		

I certify that this request represents a reimbursement of actual costs incurred during the invoice period and that these costs are appropriate and in accordance with this Subaward. The COLLABORATOR further certifies that payment made by UTHSCH under this Subaward shall not duplicate reimbursement of costs and services that are received from other sources.

Signed: _____
Project Director/designated signatory

Approved for payment: _____
COLLABORATOR/authorized financial official

7.2 Progress Reports

7.2.1 HCC Annual Report

The HCC will submit an annual report which will include all study activity (clinical, regulatory and financial) to f each calendar year.

7.2.2 Clinical Site Reports

Each participating clinical site will submit an annual report to the HCC. The following template is to be utilized to complete the annual report. The deadline for the annual report is October 1st to the HCC. The time period for the annual report is September 15th of the previous year to September 14th of current year. The report should be emailed to Erin.E.Fox@uth.tmc.edu.

Non-Compressible Torso Hemorrhage (NCTH) Annual Report TEMPLATE

Clinical Site:
Contractor:
Principal Investigator:
Dates:

Budgetary:
Changes to Personnel since the previous annual report are listed below:
Personnel _____ Role _____
(*Will be listed as necessary. Once personnel is listed as added, they do not need to be listed again, unless their % effort changes or they are removed from the grant funding.)*

Expenditures:
(*Equipment and travel purchases and summaries of other expenditures will be outlined here. Please list actual dollar amounts and ensure they coincide with the invoices sent to UTHouston.)*

Protocol/Enrollment:
(Protocol updates will be listed here. Once the study is enrolling, recruitment will be tracked.)

Presentations/Publications:
(Please cite W81XWH-14-1-0112 on any publication or presentation that is NCTH related. Any such publication, abstract or other presentation should be listed here.)

Communication/Meetings:
(*Indicate the frequency and type of NCTH related communication and meetings that have occurred at your center or at another site.)*

Other Comments/Updates:
(Miscellaneous information will be stated here.)

Chapter 8: Regulatory

Purpose: To inform the study staff of the regulatory requirements for the study, to review the process for institutional approval, maintenance of all regulatory documentation at sites and HCC, and close out procedures.

8.1 IRB Submission Process

8.1.1 Initial IRB Submission

The University of Texas Health Science Center Committee for the Protection of Human Subjects (CPHS) will be responsible for the overall regulatory management for NCTH.

Each site will be responsible for submission of the NCTH protocol, other study documentation, and the UT CPHS approval letter to their local institution's Institutional Review Board for review and approval. Each site is expected to comply with their local regulatory guidelines regarding screening, enrollment, consenting and follow up.

In the event the site is required to obtain consent, the coordinator will forward a copy of the informed consent to be used for review and approval by the HCC prior to IRB submission.

Once the site's IRB has approved the study, the approval letter will be forwarded to the HCC.

8.1.2 Continuing Review Process

The HCC and each site will be responsible for submitting all necessary study documentation in a timely manner to ensure the study remains open at the site until all study procedures and data analysis has been completed.

The HCC will be responsible for providing any updated study documentation including protocol amendments, revised CRFs, overall study enrollment information, and HCC continuing review approval letter.

The sites will be responsible for submission of the continuing review application/paper work prior to the current IRB expiration date to allow for adequate time for the IRB committee to review. The site personnel will forward the updated continuing review approval letter to the HCC.

8.1.3 Other IRB Communication

The site will notify the HCC of any communication with the IRB regarding unanticipated events or subject complications related to the study.

8.2 End of Study Procedures and Record Retention

The site Principle Investigator (PI) or designee is responsible for:

1. Receipt, maintenance, storage, and availability of the regulatory documents binder once the study is underway.
2. Storage of all study records in an appropriately secured location for a period specified by institutional policy, state or federal regulations, or for a minimum of at least two years following FDA notification of study completion.
3. After completion of the study, if on-site record storage is impractical; records may be stored in a

secure off-site facility provided the records are readily accessible in the event of an audit.
4. In the event the PI leaves the clinical site; the PI is responsible to provide the HCC with written notice of the location of study records and the name and phone number of an alternate contact in the event of an audit.
5. The site PI or designee is responsible for ensuring site personnel are trained on this SOP. Such training will be documented on the site training log.

The Houston Coordinating Center (HCC) is responsible for:
1. Collection, organization, and providing regulatory documents to clinical sites at the outset of the study.
2. Establishing and maintaining a tracking system for the timely update of clinical site regulatory documents.
3. Routine communication with clinical sites on regulatory documents with pending expiration dates and collection of updated documents.
4. Providing centers with a date of destruction for clinical research records, if not otherwise specified by local site policies/procedures.

Procedures
Regulatory Documents
1. The HCC will provide clinical site research coordinators with regulatory documents binder templates.
2. The site research coordinators will ensure that the appropriate documents are placed in the regulatory documents binders on a regular basis and maintained in a secured area with restricted access. The research coordinator will make the binders available for review by the monitor at each site visit.
3. The HCC will work with the research coordinator at each center to ensure documents are complete and current.
4. The HCC will keep electronic copies of all documents received by the centers and will keep any hard copies received in a locked and secured area with restricted access.

Source Documents, Consents, and CRFs
1. The research coordinator or delegate will transcribe the appropriate data from the source documents into each subject's case report form for entry into the eCRF.
2. The research coordinator will ensure that all source documents, consents, and CRFs are stored in a secure location with access limited to research team members, (i.e., monitors from one Sponsor/CRO may not see study documents from another study).
3. The method of clinical documentation at each site (i.e. electronic EMR vs. paper clinical record) may necessitate a separate folder of source documents for completion of the CRF.
4. The HCC study Monitor will review study document security as needed.

Contracts and Financial Records
The research coordinator will store contracts, budgets, and infrastructure documents apart from subject records, in a secure location with access limited only to research team members.

Chapter 9: Training

Purpose: To provide training materials to be used at each site for research and clinical staff to understand subject screening, direct observation, data collection and data entry into the web based database.

9.1 Research Staff

All clinical research staff involved with NCTH must be trained to:

- Screen all eligible patients
- Assess the patients upon ED arrival for eligibility
- Complete direct observation data collection on all eligible subjects
- Communicate with pre-hospital air ambulance staff to obtain pre-hospital information
- Understand the definition of anatomic hemostasis and resuscitation
- Communicate with clinical staff/physicians to obtain hemostasis and resuscitation date & times
- Complete data entry into study web based database

9.2 Clinical Staff (including pre hospital staff and physicians)

All clinical staff involved with NCTH will be trained to:

- Understand the purpose of this prospective, observational study
- Understand the screening and enrollment criteria
- Understand the definition of anatomic hemostasis and active resuscitation
- Communicate with the research team regarding times and events throughout direct observation time frame

9.3 Training Materials
9.3.1 One page summary

Non-Compressible Torso Hemorrhage (NCTH)

Study Design: Multicenter, prospective, observational study which includes 4 level 1 Texas trauma centers. The centers will screen patients transported to the Level 1 center and enroll the patients who meet the criteria for non-compressible torso hemorrhage.

Eligibility Criteria:

Inclusion:

- 15 years of age or older or ≥ 50 kg body weight if age unknown
- Has a truncal procedure (endovascular or open) **within 4 hours** of emergency department (ED) arrival.
- Admitted to one of four participating Level 1 trauma centers

Exclusion:

- Prisoners directly transported from a correctional facility

Screening/Enrollment: Research staff will be available in-house 24/7 to screen all patients transported (directly from the scene or transferred from another facility) for non-compressible torso hemorrhage injury who meet the eligibility criteria. If the patient meets the eligibility criteria, the research staff will follow the subject with direct observation until initial resuscitation has been achieved or until care is determined futile or subject expires. Indirect data collection will continue through the in-hospital stay up to time of discharge of day 30, whichever occurs first.

Data Collection: Elements to be collected will include injury information, vital signs, standard of care laboratory values, initial resuscitation products and fluids, lifesaving interventions, initial torso vascular procedures, complications, discharge disposition, and injury severity scores.

Research staff will be asked to round on all directly observed subjects on a daily basis while in hospital to monitor for complications.

Objective: This study will determine current practice patterns for the treatment of patients with non-compressible torso hemorrhage.

9.4 Helpful tips

- Recommend frequent and ongoing training prior to and throughout subject enrollment
- Monitor each individual's performance on a regular basis and retrain as needed
- Document attendance at training meetings – use training log to document names, signatures, date of training
- Remember to train new residents and staff at the beginning of each rotation change

- Provide updates to all people involved following the patient's enrollment – let them know the positives and negatives of the process and how to adjust

Chapter 10 – Publication Policy –

NCTH

Publication Committee Guidelines

The following guidelines have been established by the NCTH Publication Committee for the publication of data collected under the protocols entitled: 1) Hemorrhage Control for Major Traumatic Vascular Injuries Phase I: A Prospective Observational Study of Non-Compressible Torso Hemorrhage (NCTH) and 2) Hemorrhage Control for Major Traumatic Vascular Injuries Phase II: A Retrospective Analysis of Non-Compressible Torso Hemorrhage. Both datasets are maintained by the Houston Data Coordinating Center (HDCC) and are referred to in this document as NCTH data. These guidelines refer to multi-center data only and not site specific data. Once the database is locked for analyses and the primary study publication is completed, the HDCC will follow current DoD guidelines related to archiving de-identified data and making it publicly available. As of September 1, 2016, the DoD is finalizing rules for making data from their funded studies publicly accessible. Until the final rules are published, we are proceeding as if the DoD will require a publicly available dataset.

In developing criteria for authorship, these guidelines address three major types of manuscripts. **Primary manuscripts** are those that report the conduct and outcome of the major objectives of the trial (i.e. the major results of the collaboration). **Secondary manuscripts** refer to secondary hypotheses and ancillary analyses that come from data that were collected for this study. **Tertiary manuscripts** are those in which data collected are used as an illustrative example of a proposed preferred methodology or studies for which ancillary data, unrelated to the primary study hypotheses, are collected, sometimes on only a subset of study sites. All data presentations, including abstracts, oral presentations, and posters, are encompassed by the term "manuscript."

General Principles

1. These guidelines may be subject to ongoing interpretation by the Publication Committee. Experience and new insights from this trial may necessitate periodic modification by consensus of the Publication Committee.

2. Any member of the Publication Committee can request that the Administrator call an anonymous vote.

3. No NCTH data shall be presented, submitted or published in any way without the express prior written approval of the Publication Committee until the data become publicly available.

4. Authorship should be based on appropriate effort as defined in the guidelines published by the International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org/roles_a.html). Authors should meet all four of the following criteria:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

5. The primary manuscript will be authored by a named group of authors who contributed significantly to its writing and the NCTH Study Group as an author. Including the NCTH Study Group allows for all members to be indexed as authors (not contributors) in PubMed. The list of members in the NCTH Study Group (including preferred name and correct degrees) is below. Responsibilities and tasks for the primary manuscript will be determined by the Houston Clinical Coordinating Center (HCCC).

6. Both retrospective and prospective NCTH datasets in their entirety will be available for use by all members of the Publication Committee, attendees of the Delphi meeting and all designees.

7. Secondary and tertiary manuscripts are strongly encouraged and may be initiated by any participating investigator or a third party at the same institution (e.g., junior faculty, graduate student, resident, post-doc, etc.). Manuscript proposals are not required to be approved by the Publication Committee. However, to minimize overlapping projects, before beginning a new analysis, please send a completed 2 page proposal form found in Appendix A to Erin Fox at erin.e.fox@uth.tmc.edu and she will check the list for overlap and notify the other interested investigators of the potential collaboration. It will be up to the potential co-authors to work out a plan for the analysis and development of a manuscript. If there are any disagreements among potential co-authors, it is the investigators' responsibility to bring it to the Publication Committee for discussion and resolution. If no overlap is evident, the new analysis will be added to the list of analyses and emailed to the NCTH investigators. All abstracts, manuscripts, posters, and other data presentations must be approved by the Publication Committee until the data are publicly available. The Publication Committee encourages collaboration with other investigators and early consultation with statisticians and epidemiologists at the HDCC, HCCC or a local institution.

8. Each secondary and tertiary manuscript proposal will identify a primary author/writing group leader, who will be responsible for assigning tasks to members of the writing group. The writing group will consist of NCTH investigators and co-investigators who have indicated interest and other HDCC/HCCC/ site personnel designated by the primary author. To uphold the authorship criteria presented in General Principle 4, it is expected that primary authors will delegate writing responsibilities early enough so that all members of the writing group are given the opportunity to contribute substantively. The primary author will determine the order of authorship. There is no prescribed limit of authors from each institution; however, each named author must have contributed significantly to the manuscript as described above. If there is a disagreement among the potential co-authors, the Publication Committee will determine inclusion of an author and/or order. For secondary (and possibly tertiary) manuscripts, the author list will

include the named authors followed by "on behalf of the NCTH Study Group." The names of all members should be included in the acknowledgements section (or however the journal prefers it) so that the contributors can be indexed as contributors in PubMed.

9. Before submission of an abstract to a scientific meeting, it is expected that the associated data analyses and interpretation will be completed. The abstract will be circulated via email prior to submission.

10. Using NCTH data as preliminary data for grant submission by investigators at participating institutions is encouraged. However, any data tables included in a grant proposal must be approved by the Publication Committee before submission.

11. Proposals for single-site analyses of NCTH data will be handled the same way as multi-site analyses until the NCTH data have been made public.

12. Following completion of the primary manuscripts and any known planned secondary and tertiary articles, the Publication Committee may consider requests from unrelated third parties for access to study data for research and publication purposes. The agreement of the Publication Committee will be set forth in writing to the third party, and all parties obtaining access to the data will agree to abide by the obligations set forth herein including Publication Committee review of planned submissions.

13. All authors are responsible for notifying the Publication Committee (via Erin Fox at the HCCC, erin.e.fox@uth.tmc.edu) of all accepted manuscripts, abstracts, and oral and poster presentations, as well as the journal, date of publication, page number(s) and other information necessary to reference the publication/presentation. The HCCC will maintain a central list of all accepted abstracts, presentations and publications relating to NCTH.

Acknowledgements

1. As this study was sponsored by external sources an acknowledgement is required on all publications.
    a. "The Non-Compressible Torso Hemorrhage (NCTH) study was sponsored by the U.S. Department of Defense (W81XWH-14-1-0112). The opinions or conclusions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the sponsor. This manuscript has been reviewed by the NCTH Publication Committee for scientific content and consistency of data interpretation with previous NCTH publications."

    In general, all articles should acknowledge support from the study sponsor, DoD, unless advised by the sponsor that acknowledgement is not necessary.

2. Contributions from other collaborators, including laboratory, economists, scientists, consultants

or other individuals providing expertise during the trial design, conduct and manuscript processes but not members of the official NCTH Study Group and not meeting the prescribed authorship criteria should also be listed in the acknowledgments.

3. If a manuscript or abstract is not approved by the NCTH Publication Committee and the authors wish to proceed to publish, the authors will include the following language in an acknowledgement:

   The Non-Compressible Torso Hemorrhage (NCTH) study was supported by the U.S. Department of Defense (W81XWH-14-1-0112). This manuscript was not approved by the NCTH Publication Committee. The opinions or assertions contained herein are solely those of the authors, and are not endorsed by NCTH or the sponsors and does not reflect the opinions or conclusions of either.

Publication Committee Members

Voting Members:

John B. Holcomb, MD	UTHealth/ CCC	john.holcomb@uth.tmc.edu
Ramyar Gilani, MD	BMC	rgilani@bcm.edu
Brian Eastridge, MD	UTHSCSA	eastridge@uthscsa.edu
Jennifer Gurney, MD	USAISR	jennifer.m.gurney.mil@mail.mil
Stacia M. DeSantis, PhD	UTHealth/DCC	Stacia.M.DeSantis@uth.tmc.edu

Non-voting members:

Erin E. Fox, PhD (Administrator)	UTHealth/ CCC	erin.e.fox@uth.tmc.edu
Jeanette Podbielski, RN	UTHealth/ CCC	Jeanette.M.Podbielski@uth.tmc.edu
Charles E. Wade, PhD	UTHealth/ CCC	Charles.e.wade@uth.tmc.edu

Appendix A

NCTH

Proposal Request Form

Instructions: A completed and approved proposal request form is required to be submitted to the HCCC and should be about 2 pages long. Authors are encouraged to contact the HDCC to receive assistance with the statistical analysis plan. Clinical site statisticians are also encouraged to participate in these consultations. All aspects of manuscript development will be governed by Publication Committee Guidelines. Proposals should contain the following elements:

1. Authors
2. Designation [Primary, Secondary, or Tertiary]
3. Tentative title
4. Background/rationale
5. Hypothesis(es) to be tested
6. Basic statistical analysis plan [and power estimate, if needed]
7. References

Appendix 5. Quad Chart

Hemorrhage Control for Major Traumatic Vascular Injuries

EDMS: 5840 and Quad Chart for Year 2 Annual Report
W81XWH-14-1-0112

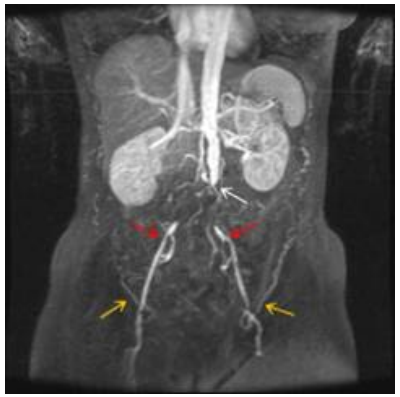
PI: John B. Holcomb, M.D. **Org:** University of Texas Health Science Center at Houston **Award Amount:** $1,991,317

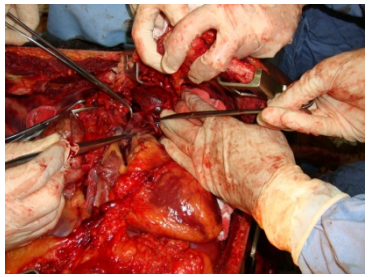
Study Aims

- Determine current practice patterns for the treatment of patients with non-compressible torso hemorrhage (NCTH) among 4 clinical sites using a retrospective study design;
- Conduct a 2-day Delphi Panel meeting of military and civilian experts to gain consensus regarding anatomic, technology, credentialing, competency, and training issues for catheter-based hemorrhage control and inform the development of the prospective study.
- Conduct a 4-site prospective observational study to test the hypo-thesis that less-invasive device-driven and expert-let hemorrhage control techniques improve survival in NCTH patients and definitively inform development of catheters, devices and training required for catheter-based hemorrhage control.

Approach

This is a 2-phase study which will include a retrospective study and Delphi Meeting in Phase I, then a prospective study in Phase II informed by the Phase I activities.





These pictures represent the care of the severely injured NCTH patient, which will be studied in this project.

Accomplishments this year: Phase I, completed retrospective study, held Delphi Panel meeting, submitted abstract to EAST, drafted manuscript, initiated CT measurement substudy at UTHealth, negotiated Data Use Agreements with Delphi Meeting attendees. Phase II, submitted site IRB application for prospective study at 3 sites, received approval at 1, drafted MOO, modified contracts with external sites for prospective study.

Timeline and Cost

Activities	Y1	Y2	Y3 Q1	Y3 Q2	Y3Q3	Y3Q4
Phase 1 milestones	→	→				
Obtain IRB approvals for prospective study		→	→			
Conduct prospective study			→	→	→	→
Data analysis/ publication						→
Estimated Budget ($K)	**994**	**996**	**EWOF**	**EWOF**	**EWOF**	**EWOF**

Updated: October 13, 2016

Goals/Milestones

CY14 -15 Goals – Phase I

- ❑ Obtain DoD HPRO and local IRB approvals
- ❑ Conduct retrospective data collection
- ❑ Analysis of retrospective data
- ❑ Hold Delphi Panel meeting

CY15-16 and EWOF Goals – Phase II

- ❑ Obtain regulatory amendment approvals for prospective study
- ❑ Conduct prospective observational study
- ❑ Data Analysis/Publications

Comments/Challenges/Issues/Concerns

- The timeline for the project has changed slightly. The prospective study be performed in an EWOF Year 3.There are no financial or scientific concerns.
- **Budget Expenditure to Date**

Projected Expenditure: Y2Q4 $249K; YTD $996K; ITD $1,991K
Estimated Actual Expenditure: Y2Q4 $76K; YTD $543K; ITD $858K